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Editorial

Medicine and Physics

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It must first be said that it was with a mixture of anticipation and reluctance that I, a physics professor by trade, agreed to write an editorial for this learned medical journal. This feeling was undoubtedly related to the fact that physical scientists have, until quite recently, felt rather unwanted in medical circles. Even now, an improvement in relations is only slowly spreading across the spectrum of our ordinary contacts, and is engendered by the circumstance that modern medicine seems to be concerning itself more and more with the physical, as distinguished from the chemical, structure of the body. This seems not to be an easy development, since the training of the average physician leaves him, on graduation from medical school, far more expert in organic chemistry than in any other area of the physical sciences. And indeed, much of what we know about the functioning of the human body is dominated by a recognition of the body's extraordinary ability to do complicated organic chemistry. It will be argued here that a rather more sophisticated training in physics than is standard among physicians might well open areas of research now closed. Alternatively, one can hope for a relaxation of the jealous protection given to medical research as the exclusive province of physicians. Indeed, as our understanding of the human body becomes deeper, this is inevitable as a result of the sheer mass of specialized information that will be required to do useful work.

We will want to touch briefly on a few areas in which physics makes contact with medicine. They are not the only ones, but they are representative of places where it may well be that the contact could be more fruitful than it now is.

The first of these is the area of instrumentation, for either diagnosis or research. This is, in fact, where I have had the most direct experience. All instruments, being inanimate objects, are constructed according to the principles of physics, and some of them even determine physical properties of the body.

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Of these instruments, probably the least sophisticated (and perhaps the most important) is the ordinary clinical thermometer. The measurement of temperature is the simplest physical determination one can make on a body, using an instrument of slightly more subtlety than a ruler or a scale. Further along, there are the x-ray machine and the electrocardiograph. These are sufficiently electronic to ensure that the average physician has only a limited understanding of their operation. Fortunately, however, they can be packaged (like a modern car) so that one need not know what is behind the shiny exterior in order to be able to operate them usefully and effectively. To use radioactive tracers, on the other hand, one must know something about them, so that their use is not so widespread in this era of easy availability as it could profitably be. The point is that the complexity of the instrumentation seems to be determined by the capacity of the physician, not normally well trained in physics, and it seems not to go an order of magnitude past that. The question is: should it? I have had some recent personal contact with research in ballistocardiography, and was at the time appalled at the extent to which the lack of adequate instrumentation has prevented the kind of progress in the subject that is necessary to turn it into a reliable clinical tool. Much of the controversy in the field derives from the fact (this will surely bring in some angry letters) that few of the workers understand clearly what their own instruments are measuring, let alone those of their colleagues. This situation could be easily improved, and, to the extent that it bases itself on a rather low level of understanding of physics among physicians, it is probably not restricted to the field mentioned.

Some other areas of contact between physics and medicine immediately suggest themselves, but only one will be briefly mentioned here in order to indicate that there are fields in which development might be appreciably speeded up by a somewhat more sophisticated use of physics in medicine. The example is the whole question of the acquisition and transport of information in the body—embracing nerve conduction, the mechanism of vision, information storage and accessibility in the brain, and so forth. Indeed, our rapidly growing understanding of computing machines, if properly applied, should lead to better ways of posing the questions about the functioning of the brain. This is a point often made in popular articles, but not often seriously tested, again partly due to the substantial lack of overlap between the experts on the brain and the experts on the computing machine.

Generally, I feel that the routine training of physicians in physics is extremely weak, and not well attuned to the potentialities of physical methods in medicine. Coupled with the small number of working collaborative arrangements, both in research and in practice (only a rare, fortunate, large hospital has a physicist of any training in its radiological division), this lack has the effect of basing medicine on the post-World War I state of science. We can surely do better.

Clinical Communications

Pulmonary Stenosis With Intact Ventricular Septum and Fallot's Tetralogy: Assessment of Postoperative Results by Auscultation and Phonocardiography

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In previous communications[1,4,5] it was shown that increasingly severe stenosis exerted an opposite effect on the systolic murmur in pulmonary stenosis with intact ventricular septum and in Fallot's tetralogy. The murmur became longer and louder when the ventricular septum was intact, but shorter, softer, and earlier when a large septal defect (Fallot's tetralogy*) was present (Fig. 1). Conversely, production of mild stenosis by a successful valvotomy or infundibular resection was also shown to produce an opposite effect on the murmur in the two conditions, shortening and softening it when the septum was intact and prolonging and intensifying it in the tetralogy. The opposite behavior of the murmur with changing severity of the stenosis was attributed to the different dynamic situation in the two conditions.[1]

The purpose of this paper is to emphasize the value of auscultation and phonocardiography in evaluating the postoperative result. The severity of stenosis after a pulmonary valvotomy or infundibular resection can be assessed by the same criteria previously defined for diagnosing the preoperative severity.[5] This method will be shown to be one of the earliest and most reliable means of determining what was achieved at operation.

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*By Fallot's tetralogy, we mean severe infundibular or valvular stenosis with large ventricular septal defect and right and left ventricular pressures of the same order. Even in acyanotic cases the stenosis is relatively severe, permitting bidirectional ventricular shunt or, at most, a small left-to-right shunt at rest.

The different effects of the three operations for Fallot's tetralogy on the systolic murmur will be used to support the thesis that in the tetralogy the length of the murmur is inversely related to the severity of the stenosis, provided the septal defect is large and the systemic resistance constant.[1,3] A successful valvotomy or infundibular resection (Brock operation) alone causes great lengthening of the murmur, since the stenosis has been rendered mild, whereas the septal defect remains unchanged. A successful Blalock-Taussig operation fails to lengthen the murmur, since both stenosis and septal defect remain unchanged. A successful repair operation with closure of the defect and removal of the stenosis produces a short ejection systolic murmur of mild stenosis with intact ventricular septum or possibly no murmur at all.

MATERIAL AND METHODS

The effect of surgery on the auscultatory and phonocardiographic findings was studied in 19 cases of pulmonary valvular stenosis submitted to valvotomy and 3 cases of infundibular stenosis with functionally intact ventricular septum submitted to infundibular resection. There were 24 cases of Fallot's tetralogy. Of these, a pulmonary valvotomy, infundibular resection, or dilatation (Brock operation) was performed in 13, a Blalock-Taussig operation in 7, and 4 had the septal defect closed and the stenosis resected.

Full clinical examination with special attention to auscultation was carried out independently by us, after which, data were compared and finally checked with the phonocardiogram. The examinations were frequently repeated before and after surgery. Particular attention was directed to the intensity and duration of the systolic murmur at the site of its maximal intensity. The intensity was graded 1-6, and the duration analyzed by noting whether the crescendo occurred in early, mid, or late systole, whether the murmur ended before, at, or extended beyond the aortic component of the second sound, and whether this sound was clear, partially buried, or obscured by the murmur. The presence or absence of splitting of the second sound was noted, and, if present, the degree of splitting during held expiration and the intensity of each component noted. The first sound was studied during respiration and held expiration for its intensity, width of splitting, and presence or absence of pulmonary and aortic ejection sounds.[1] The presence or absence of sounds and murmurs in diastole was also noted.

High-frequency (logarithmic) sound tracings which give an accurate graphic representation of human hearing[8-10] were recorded in every case before and after surgery and frequently repeated from time to time. A modified two-channel Sanborn Stethocardiette was used in the early cases but a six-channel N.E.P. recording apparatus was later substituted. Sound tracings were recorded synchronously with ECG, indirect carotid and jugular tracings. In most cases, sound recordings were repeated during cardiac catheterization to obtain synchronous phonocardiographic, right ventricular, or pulmonary arterial tracings. Recordings were made at the mitral area, fourth left intercostal space at the left sternal edge, third left intercostal space, pulmonary area, and aortic area. Pre- and postoperative sound recordings were always made at the same amplification during held expiration. This method was roughly quantitative when used on the same patient, provided no marked changes occurred in the thickness of the chest wall, but a method of sound calibration would have been desirable.

Tracings recorded at high speed (80 mm. per second) were essential for accurate study. Mitral and tricuspid components of split first sounds, aortic and pulmonary ejection sounds, and aortic and pulmonary components of split second sounds were identified by methods previously described, and always measured during held expiration unless otherwise stated. The intervals were always measured from the onset of the deflections, whether recorded in the phonocardiogram, electrocardiogram, indirect or direct pulse recordings.

The systolic murmur was analyzed in suitable recordings made during expiration at the site of maximal intensity of the murmur. The crescendo and duration of the murmur were measured from the first component of the first sound to the peak and the end of the murmur, respectively.

The time taken for the systolic murmur to reach its crescendo was expressed as a percentage of the time between the first heart sound and the aortic second sound (left ventricular systole). Thus, if the crescendo ended in midsystole, it would be expressed as 50 per cent, whereas if it occurred at the aortic second sound it was 100 per cent. Similarly, the total duration of the murmur was expressed as a percentage of the time between the first heart sound and the aortic sound, and if it extended beyond the aortic sound, some figure exceeding 100 per cent would be obtained (Fig. 1). All measurements were made in at least ten separate systoles, and the mean was taken.

Pre- and postoperative severity of valvular or infundibular stenosis with intact ventricular septum was confirmed in most cases by the right ventricular pressure, whereas in the tetralogy a clinical method was used. These will be discussed in detail below under the appropriate headings.

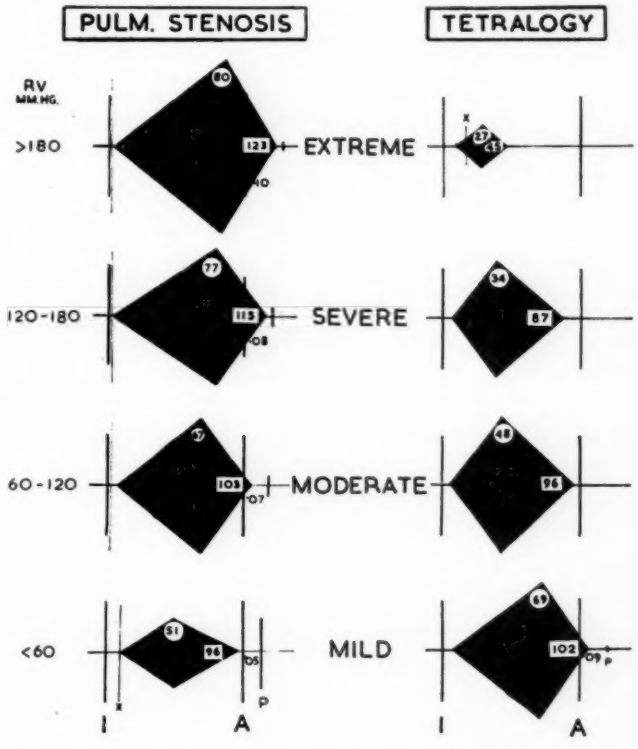

Fig. 1.—This diagram depicts the opposite effect induced on the length of the murmur by increasingly severe stenosis in pulmonary stenosis with intact ventricular septum and Fallot's tetralogy. The mean time of the crescendo and duration of the murmur, each expressed as a percentage of the duration of left ventricular systole, is indicated and drawn to scale for each category of severity. The mean width of the splitting of the second sound is also indicated. Increasingly severe stenosis with intact septum causes a kite-shaped murmur due to great lengthening with delay in crescendo. In severe stenosis the murmur usually engulfs the aortic second sound (*A*) but always ends before the soft delayed pulmonary component (*P*). Increasing severity in the tetralogy causes the murmur to become shorter, softer, and more confined to early systole, and in extreme cases an aortic ejection sound usually emerges. A very much delayed pulmonary component producing wide splitting is heard only in mild cases. (From Vogelpoel and Schrire,[5] 1960, courtesy of Circulation).

PULMONARY STENOSIS WITH INTACT VENTRICULAR SEPTUM

The effect of surgery on the auscultatory and phonocardiographic findings was studied in 19 cases submitted to pulmonary valvotomy. A "blind" transventricular operation was performed in 7 and an open transarterial pulmonary valvotomy in 12, using hypothermia in 5 and cardiopulmonary bypass in 7. In 4 of the latter, infundibular resection for gross secondary infundibular hyper-

trophy was required. The length of the systolic murmur and the width of splitting of the second sound was used to predict whether mild or moderate pulmonary stenosis or little change had been produced by the operation. The criteria used were those determined in a previous study[5] and summarized below (Fig. 1).

In *mild stenosis* (right ventricular pressure [RVP] under 60 mm. Hg) the murmur was soft to loud in intensity, reached a crescendo in midsystole and ended before or at the aortic component of the second sound. The second sound was usually abnormally split during expiration (average 0.05 second; range 0.02-0.09 second), and a pulmonary ejection sound was frequently present. In *moderately severe stenosis* (RVP 60-120 mm. Hg) the murmur was louder, the crescendo and duration greater, extending a short way beyond the aortic component, which it never obscured. Splitting was wider (average 0.07 second; range 0.05-0.12 second), and the pulmonary component softer. A sharp, click-like first sound was frequently heard on expiration. In *severe stenosis* (RVP 120-180 mm. Hg) the murmur was loud and kite-shaped, due to its marked prolongation and delayed crescendo. The murmur invariably extended well beyond the aortic component, which it either partially or completely buried. The murmur always ended before a very soft pulmonary component which was widely separated from the aortic component (average 0.08 second; 0.06-0.12 second). In *very severe stenosis* (RVP above 180 mm. Hg) the murmur was loud and so prolonged that it invariably obscured the aortic component. The great width of splitting (average 0.10 second; range 0.09-0.10 second) required phonocardiography for its detection and measurement, since splitting could not be heard when the aortic component was buried. Whenever the aortic component was completely buried by murmur, a right ventricular pressure above 120 mm. Hg could be predicted. The severity of infundibular stenosis with intact ventricular septum could be determined by the same criteria cited for valvular stenosis. There were only a few points of difference. In infundibular stenosis, splitting of the second sound was wider than in valvular stenosis of comparable severity, and a pulmonary ejection sound or click-like first sound on expiration was never encountered.

The assessment of the postoperative severity of stenosis made by these criteria was checked against right ventricular and pulmonary arterial pressures obtained either at operation immediately after valvotomy (not always reliable) or, preferably, by cardiac catheterization a few months after surgery. Nine cases were recatheterized, the cases being selected to cover the full range of results as predicted by auscultation. The result was considered excellent when the right ventricular pressure was reduced to below 40 mm. Hg, good if under 60 (i.e., mild pulmonary stenosis), fair if above 60 or below 100 mm. Hg (i.e., moderate pulmonary stenosis), especially if reduced from a very high level, and bad if the pressure remained above 100 mm. Hg even if reduced from a high level.

Results.—Of the 9 cases recatheterized after surgery, 5 had right ventricular pressures below 60 mm. Hg (54/0, 52/5, 52/7, 40/0, and 35/2 mm. Hg), 2 had pressures of moderate severity (82/0 and 80/0 mm. Hg), and 2 remained in the severe category (150/0 and 125/7 mm. Hg). The prediction of severity from the length of the murmur and width of splitting proved correct in these cases.

In 6 of the remaining 10 cases not recatheterized, right ventricular pressures recorded immediately after the valvotomy had to be used for proof of the success of the valvotomy. The pressures fell from 160/0 to 65/7, 196/−2 to 30/2, 125/15 to 62/4, 135/2 to 45/5, 115/0 to 90/0, and 128/0 to 60/10 mm. Hg, respectively. In the latter 4 cases, infundibular resection was considered necessary because of gross subvalvular muscle hypertrophy which caused failure of the pressure to drop below 100 mm. Hg despite complete transarterial pulmonary

valvotomy under direct vision. These cases all developed pronounced shortening and softening of the murmur, with the crescendo in midsystole, and cessation before or at the aortic component, indicating mild stenosis. Reduction of splitting was equally impressive, but required time to appreciate, since during the first few postoperative weeks the soft pulmonary component was often inaudible because of damping from pericardial reaction and other factors. For the same reason, shortening of the murmur was much more reliable than the degree of softening in the early postoperative period.

In 4 cases no postoperative pressure data were available. In one of these a good result was predicted and borne out by a 2-year follow-up, during which the cardiac symptoms, the giant A wave, and cyanosis from a right-to-left interatrial shunt disappeared. In the remaining 3 the murmurs became so short and soft that conversion to very mild stenosis seemed obvious.

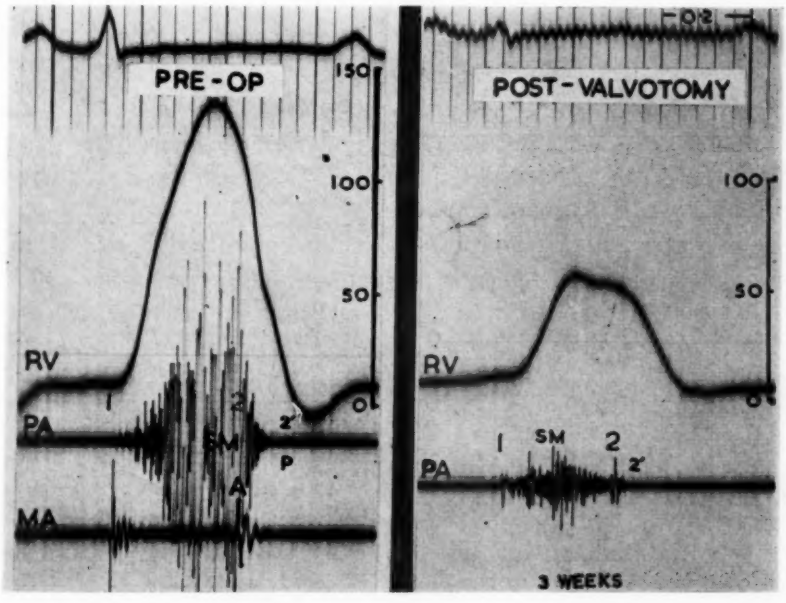

Fig. 2.—Pulmonary stenosis before and after valvotomy. This case illustrates the rapidity with which the length and loudness of the murmur and the width of splitting change after successful valvotomy, enabling early confirmation or prediction of the result at the bedside. The very loud, prolonged systolic murmur, which completely obscured the aortic sound before operation, became much shorter and much softer, ending at the aortic component soon after surgery. Splitting, which could not be heard at this early stage, had narrowed from 0.11 to 0.05 sec. Recatheterization 3 weeks after surgery confirmed the good result predicted. The RVP had fallen from 135/5 to 52/3 mm. Hg. The phonocardiograms were taken at the same site and amplification. Each vertical line in this and subsequent tracings measures 0.04 sec.

The marked shortening and softening of the murmur following successful valvotomy is shown in Fig. 2, which also emphasizes how rapidly the change develops, permitting early prediction of the postoperative right ventricular pressure. Before valvotomy the loud, prolonged, kite-shaped murmur extended well beyond and buried the aortic component, but ended before a very soft and greatly delayed (0.11 second) pulmonary component. These features indicated

marked prolongation of right ventricular systole from severe pulmonary stenosis, and the right ventricular pressure was 135/5 mm. Hg. Transarterial valvotomy under direct vision, using hypothermia and inflow occlusion, was performed, following which the murmur became much shorter and softer, and splitting narrowed to 0.05 second. These findings clearly indicated mild stenosis with little prolongation of right ventricular systole. This prediction was verified by a right ventricular pressure of 52/3 mm. Hg at recatheterization 3 weeks after valvotomy.

Fig. 9 (top row) shows the postoperative murmurs in 4 cases. In the first case the result was bad. Preoperative auscultation had shown a very prolonged murmur completely obscuring the aortic component, and the phonocardiogram revealed very wide splitting (0.14 second). The prediction of very severe stenosis was confirmed by a right ventricular pressure of 160/20 mm. Hg. Following blind transventricular valvotomy, the murmur shortened only slightly, so that the aortic component could just be heard. Splitting was still considerable (0.11 second). Central cyanosis and a giant A wave persisted. The auscultatory findings were now those of severe pulmonary stenosis, and a bad result was predicted. During the follow-up, the length of the murmur and width of the splitting remained unchanged, and cardiac catheterization 3 years after the operation confirmed the unsatisfactory pressure of 125/7 mm. Hg. A second operation, using cardiopulmonary bypass, proved that the bad result had been due to inadequate valvotomy, and not to irreversible subvalvular muscular hypertrophy.[11,14] A complete valvotomy was performed, whereupon the right ventricular pressure fell to 48/4 mm. Hg, and the length of the murmur and the width of the splitting became those of mild stenosis.

In the second case shown in Fig. 9 (top row, second from the left) the murmur extended into and partially buried the aortic second sound, and splitting was 0.07 second. The features were those of a moderately severe stenosis, and a fair result was predicted. Moreover, there was no change in the length of the murmur or width of splitting over a 2-year follow-up. The preoperative right ventricular pressure was 200/15 mm. Hg, and the postoperative pressure at recatheterization 2 years after the blind valvotomy was 80/0 mm. Hg, confirming the forecast made from auscultation. Fig. 3 shows a similar result. Although the grossly prolonged and loud murmur of very severe stenosis had shortened considerably, and a previously unrecordable pulmonary second sound had emerged, the degree of shortening was not good enough. The crescendo was in late systole, and the aortic component was partially obscured; splitting was wide (0.07 second). These were the features of moderately severe stenosis, and recatheterization 3 weeks after the open transventricular valvotomy confirmed a right ventricular pressure of 82/0 mm. Hg. During a 2-year follow-up the length of the murmur and width of splitting remained unchanged, suggesting that there had been no regression of secondary infundibular hypertrophy. This was confirmed at recatheterization, the pressures in the right ventricle, infundibulum, and pulmonary artery being 92/0, 63/0, and 25/10 mm. Hg, respectively. There were distinct gradients at valvular and infundibular levels.

Fig. 3.

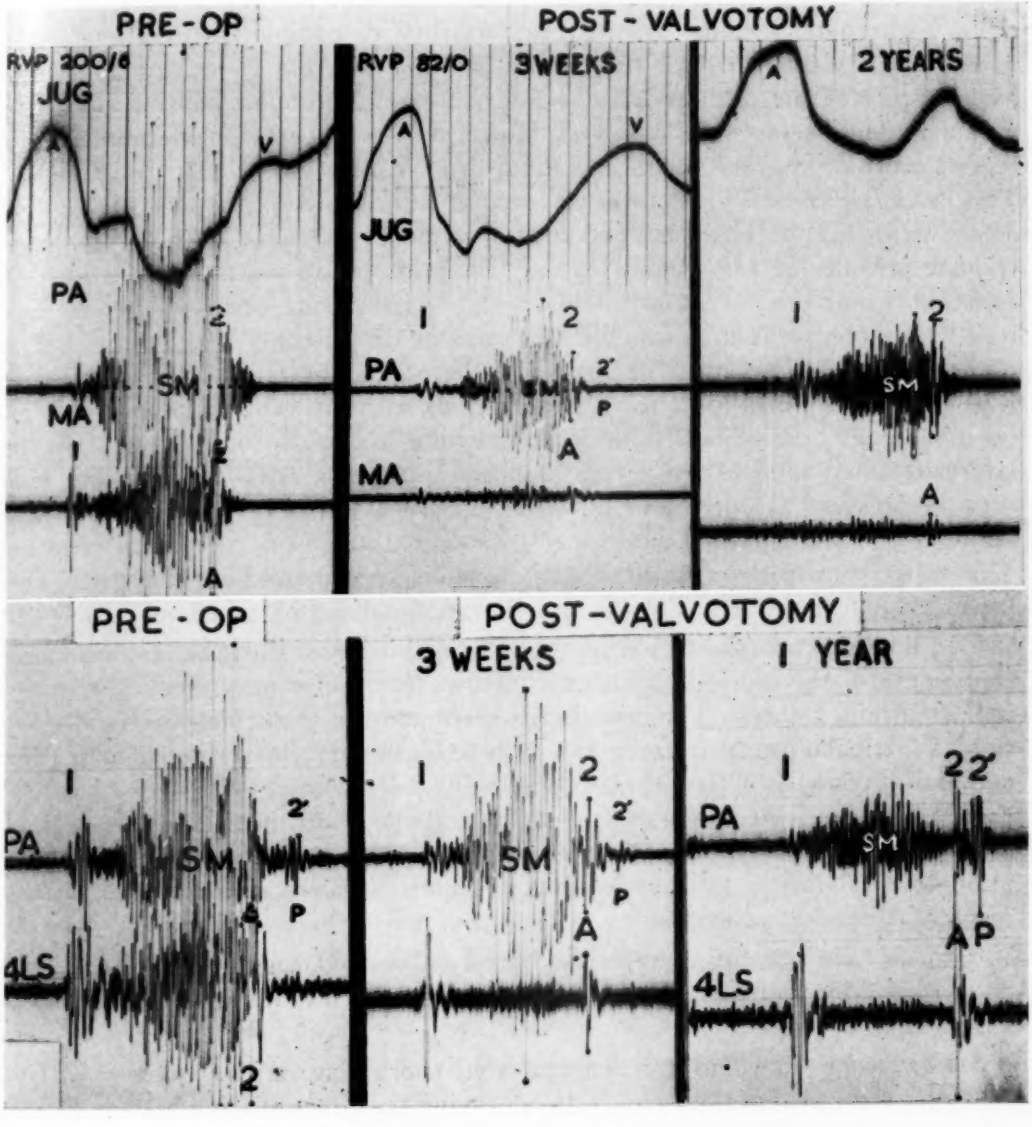

Fig. 4.

Fig. 3.—Pulmonary stenosis before and after valvotomy. Three weeks after an open transventricular valvotomy, the grossly prolonged and loud preoperative murmur of very severe pulmonary stenosis (RVP, 200/6 mm. Hg) softened and shortened, and a very soft, inaudible pulmonary component became recordable. However, only a fair result was predicted because the murmur did not shorten enough. Its crescendo occurred well beyond mid-LV systole, the aortic sound was partially buried, and splitting was wide (0.07 sec.), all suggesting moderately severe stenosis and confirmed by a RVP of 82/0 mm. Hg at 3 weeks after surgery. Follow-up for 2 years failed to show any further shortening of the murmur, and the pulmonary sound remained inaudible, suggesting persistence of high RVP from incomplete valvotomy. Pre- and postoperative phonocardiograms were recorded at same amplification in this and subsequent tracings.

Fig. 4.—Spontaneous regression of secondary infundibular stenosis after successful valvotomy, shown by gradual shortening and softening of the murmur, narrowing of the split second sound, and return to normal intensity of the pulmonary component. See text for details.

Gradual regression of secondary infundibular hypertrophy may occur after successful valvotomy. Such cases initially have a disappointing drop in right ventricular pressure despite the certainty of complete valvotomy done under direct vision. Brock[12] has attributed this to gross concentric muscular hypertrophy of the outflow tract, which causes infundibular stenosis once the valvular stenosis has been relieved. However, the hypertrophied muscle may regress with time, resulting in a gradual drop in right ventricular pressure.[11,14] This favorable trend is detectable by serial auscultation and phonocardiography, as shown in Fig. 4. This case had severe pulmonary stenosis with a right ventricular pressure of 135/4 mm. Hg and the appropriate murmur and width of splitting. Complete valvotomy under direct vision, using cardiopulmonary bypass without hypothermia, resulted in a pressure drop to only 70/0 mm. Hg. The outflow tract was hypertrophied when palpated via the pulmonary artery, but was not judged to be sufficiently stenosed to warrant ventriculotomy and infundibular resection. The length of the murmur and width of splitting 3 weeks later suggested moderately severe stenosis in keeping with the disappointing drop in pressure at operation. However, 1 year later, both length of murmur and width of splitting had diminished to a degree suggesting very mild stenosis. This was confirmed by recatheterization, which now showed a right ventricular pressure of 40/0 mm. Hg. The ultimate result was therefore excellent.

In the third case shown in Fig. 9 (top row, third from the left) the postoperative length of the murmur, width of splitting, and pulmonary ejection sound[6,7] indicated mild stenosis. The good result predicted was confirmed by the drop in right ventricular pressure from 135/5 to 52/3 mm. Hg, determined at cardiac catheterization. In the last case shown in Fig. 9 (top row, fourth from the left) the murmur became very soft and short, and the width of splitting was much reduced (0.05 second). These features were those of very mild stenosis, or even idiopathic dilatation of the pulmonary artery without stenosis, and such a result was considered excellent.

In no case was the murmur completely abolished, and in only 2 cases did the reduction in width of splitting on expiration return to normal (0.03 second or less).

Comment.—The findings demonstrated shortening of the murmur in proportion to the relief of the stenosis, thus proving the direct relation between length of murmur and severity of the stenosis when the ventricular septum is intact. The direct relation between width of splitting and the severity of stenosis was likewise demonstrated, confirming the observation of Leatham and Weitzman.[7] The findings also show that the auscultatory changes, especially the length of the murmur, give an early indication of the surgical result. Notable shortening of the murmur may be detected on the operating table after completion of the valvotomy. It can certainly be appreciated in the pulmonary area during the early postoperative period and readily recorded by phonocardiography shortly thereafter, permitting a prediction of the postoperative severity of the stenosis long before this can be done by the electrocardiogram or x-ray, both of which reflect the trend much more slowly and with less reliability. This stands to reason

because the murmur and width of splitting reflect dynamic phenomena (duration and pressure of right ventricular systole) which quickly change after valvotomy, whereas the electrocardiogram and x-ray take much longer to show signs of improvement since they reflect changes in the anatomic state of the right ventricle.

The auscultatory signs were of considerable value to us in the earlier cases in which blind transventricular valvotomies had been performed. In the cases in which valvotomies had been performed under direct vision, and pressures measured thereafter, there was less use for the auscultatory signs. However, they did add important confirmatory evidence, since postoperative pressures were not always reliable. It is believed that the signs will have considerable practical application in detecting whether or not regression of secondary infundibular stenosis is taking place in those cases in which this complication is known to be present. For this reason, we routinely record sound tracings at the same site and amplification during follow-up in order to obtain serial phonocardiograms.

INFUNDIBULAR STENOSIS WITH INTACT VENTRICULAR SEPTUM

Only 3 cases of infundibular stenosis with intact ventricular septum were submitted to infundibular resection. Two had very severe stenosis, with proximal right ventricular pressures exceeding 200 mm. Hg; in the third case the right ventricular pressure was 115/0 mm. Hg. Open-heart surgery under hypothermia was used in the first case, and cardiopulmonary bypass in the last 2 cases. The very severe cases both had minute ventricular septal defects, but in one the defect was distal to the stenosis. The defects were so small as to render the ventricular septum functionally intact, and their presence was undetectable.[5]

In the first case the preoperative auscultatory findings revealed very gross prolongation of right ventricular systole, with a systolic murmur extending far beyond the aortic second sound, which it completely drowned. There was no recordable pulmonary component. As predicted, the stenosis was very severe (right ventricular pressure, 212/5 mm. Hg). Direct pressure recordings immediately following resection showed no fall in the right ventricular pressure. However, auscultation during the early postoperative period clearly revealed considerable shortening of the murmur, with an audible aortic component, and the phonocardiogram 2 weeks after surgery showed the emergence of a pulmonary component 0.05 second after the aortic sound (see Fig. 9, Vogelpoel and Schrire[5]). From the auscultatory findings, the right ventricular pressure was predicted to be just below 100 mm. Hg; and on recatheterization 3 weeks postoperatively the right ventricular pressure was 70/6 mm. Hg, and a small left-to-right ventricular shunt was demonstrated. The observations in this case proved that in infundibular stenosis with functionally intact ventricular septum the duration and pressure of right ventricular systole are directly related to the severity of the stenosis, as in valvular stenosis with intact ventricular septum. Thus, the murmur shortened and softened after resection, which was the reverse of what would have happened had a large septal defect (Fallot's tetralogy) been present (see below).

The result in the second case was excellent, because complete resection of the stenosis was possible using the heart-lung machine. Before operation the murmur was extremely prolonged, extending well beyond the aortic second sound, which it completely buried, and ended before a very soft pulmonary component, which was greatly delayed (0.14 second) (Fig. 5). These features denoted grossly prolonged right ventricular systole and, hence, very severe stenosis. This was confirmed at catheterization, the proximal right ventricular pressure being 220/0 mm. Hg, whereas there were two levels of pressure in the infundibular chamber, 66/0 and 25/0 mm. Hg, the pulmonary arterial pressure being 25/6 mm. Hg. The patient was an acyanotic, well-built man of 32, with mild dyspnea. At ventriculotomy, severe infundibular stenosis was found. There was a small septal defect (2 mm. in diameter) in the infundibular chamber, the septum proximal to the stenosis being intact. The stenosis was widely excised and the septal defect closed. The right ventricular pressure dropped to 40/0 mm. Hg. Postoperatively, no murmurs could be heard, reflecting complete removal of the stenosis. However, wide splitting of both sounds was present because of complete right bundle branch block induced by the operation.

In the third case the right ventricular pressure dropped from 115/0 to 35/5 mm. Hg after resection of infundibular stenosis. Three weeks later the phonocardiogram confirmed marked softening and shortening of the murmur, which ended at the aortic component, whereas the pulmonary component increased in loudness and the splitting narrowed from 0.12 to 0.07 second despite the production of right bundle branch block.

FALLOT'S TETRALOGY

1. *Pulmonary Valvotomy and Infundibular Resection (Brock Operation).*— The effects of surgical relief of the stenosis (pulmonary valvotomy in 7 cases, infundibular resection in 3 cases, and dilatation of the infundibulum in 3 cases) on the clinical condition and auscultatory signs was studied in 13 cases of Fallot's tetralogy. Since only the stenosis was relieved by this operation, the change in the length of the murmur could be used to predict the operative result. The auscultatory and phonocardiographic criteria used were those determined in a previous publication[5] and summarized as follows (Fig. 1).

In *extremely severe* cases of tetralogy the murmur was invariably short, soft, confined to early systole, and ending by midsystole. An aortic ejection sound was usually audible, and the second sound was loud and single. In *severe* tetralogy the murmur was usually loud but short, with its crescendo before midsystole and termination before the aortic second sound. A pulmonary second sound was never audible. In *moderate* cases the murmur was loud and longer, with its crescendo at midsystole and termination at the aortic second sound. The second sound was loud and single. In *mild* cases the murmur was loud and more prolonged, with its crescendo in the latter half of systole and extension into, and occasionally slightly beyond, the aortic second sound. Although at times loud at the aortic component, the murmur very rarely totally buried this sound. A pulmonary component was frequently recorded and often heard; it was usually extremely soft and localized to the pulmonary area. Splitting was always wide (average 0.09 second). A loud, long murmur reflected good pulmonary flow, and an audible or recordable pulmonary component indicated a relatively normal pulmonary arterial pressure.

The assessment of the postoperative severity of the stenosis based on the auscultatory signs was correlated with the surgical result, as determined by the clinical method previously described.[5] Clinical assessment of the disability and degree of cyanosis had to be depended upon, since most objective methods were unreliable in the tetralogy. Thus, the right ventricular pressure could not be used, since it failed to alter, whether a good or bad operation had been performed.

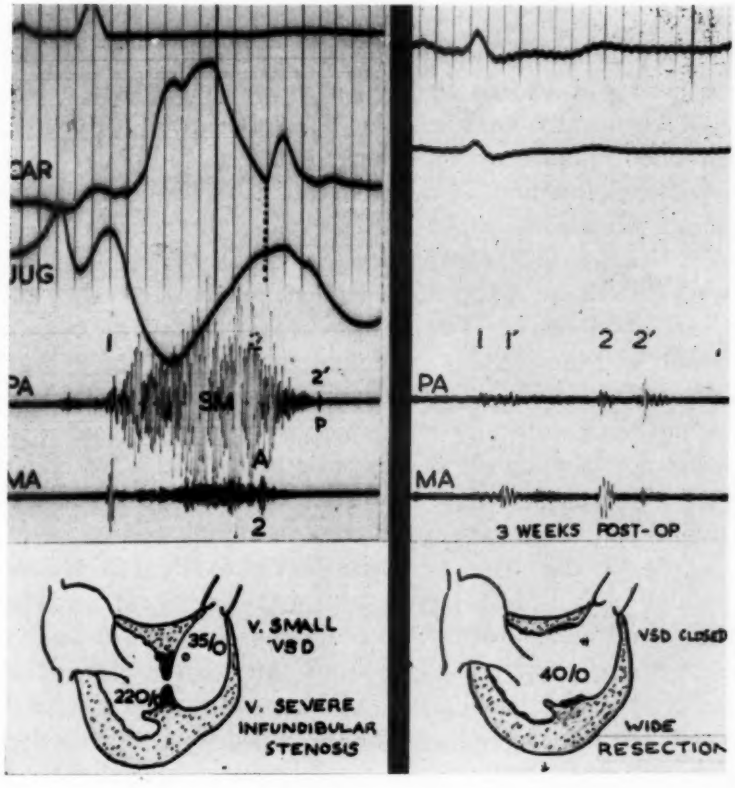

Fig. 5.—Severe low infundibular stenosis before and after complete resection. The preoperative length of the murmur and the width of splitting were greatly increased, suggesting very severe stenosis with intact septum; confirmation by pressure recordings was made at operation, as depicted in the diagram. Since there was no additional valvular stenosis, and the minute septal defect distal to the stenosis was closed, there was no residual murmur after resection. Wide splitting persisted because of complete right bundle branch block (not well shown in ECG leads used) induced by the operation.

This is because, in cases of tetralogy, the right ventricular pressure is determined by the systemic resistance and not the stenotic resistance when the septal defect is large. Consequently, pressure data, whether obtained immediately after the operation or later by catheterization, give no guide, except for a slight rise in the pulmonary arterial pressure.[17] A much better guide is the degree to which the right-to-left shunt is reduced, since the less the stenosis the less the shunt and the greater the pulmonary blood flow. The most desirable end result obtainable by this type of operation is the production of a milder grade of stenosis offering a resistance slightly less than the systemic resistance. This will permit a slight left-to-right shunt through the ventricular septal defect (usually large in the

tetralogy), so that central cyanosis disappears at rest, whereas equal pressures persist in the right and left ventricles, and the pulmonary arterial pressure rises to normal level. Such a situation, although by no means ideal, is termed excellent for this operation. It results in the disappearance of cyanosis at rest, polycythemia, clubbing and squatting, with great improvement in effort tolerance and physical development.[15,16] Slight cardiomegaly may occur.

Overcorrection of the stenosis is undesirable because it produces a severe left-to-right shunt through the large ventricular septal defect.[18,20] Although there is a temporary benefit from loss of right-to-left shunt, all the serious hemodynamic consequences of a large ventricular septal defect with a severe left-to-right shunt will eventually emerge. The development of cardiomegaly, both left- and right-sided, pulmonary plethora, enlarged pulmonary arteries, and pulmonary hypertension would all point to this undesirable result (see below).

A totally inadequate operation was revealed in time by persistence of unchanged central cyanosis, polycythemia, and disability, and such a result was naturally bad. Between a bad and excellent result were the grades of slight improvement and good result. If the grade of disability and cyanosis did not improve, the result was termed bad. A slight or poor result was indicated by only slight improvement in the cyanosis and disability. A good result was the equivalent of producing a mild tetralogy with complete return to normal of the hemoglobin, disappearance of cyanosis at rest, ability to lead a normal life (except for strenuous exertion), and freedom from symptoms.[15,16] It was thus not difficult to grade the functional result on clinical criteria alone.

Results: Of the 13 cases, the result was bad in 3, slight in 1, good in 3, and excellent in 6, although in 1 of the latter, the later "overcorrection" of the stenosis by subacute bacterial endocarditis converted the case into a large ventricular septal defect, with marked left-to-right shunt. All 3 cases showing a bad result showed no change in the length of the systolic murmur. All 6 cases with an excellent result developed a marked change in the murmur. Not only did it become much louder, but it now filled systole, extending into and slightly beyond the aortic second sound, and frequently (4 cases) the pulmonary component became recordable or even audible (Figs. 6, 9). Such cases had the same auscultatory findings described in mild tetralogy. Pulmonary incompetence developed in 2 cases.

All 3 cases with a good result developed marked prolongation of the systolic murmur, with the crescendo in the latter half of systole, and a murmur extending into the aortic second sound, but a recordable pulmonary component did not emerge. The case showing slight improvement developed only slight prolongation of the systolic murmur, but still remained in the unsatisfactory category of severe tetralogy, since the crescendo occurred before midsystole, followed by a rapid diminuendo, with the murmur very soft at the aortic component (Fig. 9, middle row, second from the left).

In 2 cases in which a bad result had been predicted in the early postoperative period, the assessment was later proved correct at necropsy. Fig. 7 illustrates one of these cases. The preoperative phonocardiogram showed an extremely short soft systolic murmur and an aortic ejection sound indicating extreme tetralogy.

Immediately after a valvotomy the murmur became more obvious, but it was soft and ended abruptly in midsystole, suggesting sudden occlusion of the outflow tract in midsystole. The aortic ejection sound could still be heard. Since these were the auscultatory signs of severe tetralogy, a bad result was predicted. The child was lost to follow-up until 3 years later, at which time the murmur still showed the same features, and the severe disability and deep cyanosis confirmed the forecast made. She died following an attempt at infundibular resection, and the necropsy specimen revealed a large septal defect with severe unrelieved infundibular stenosis, proving that a short soft murmur indicates severe stenosis in the tetralogy.

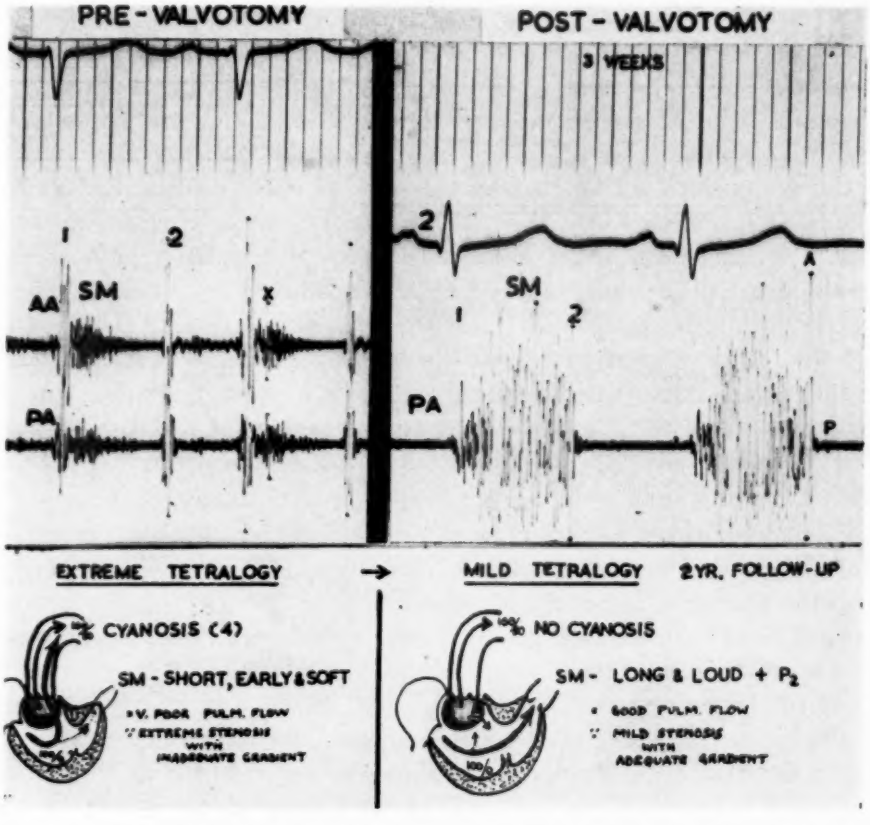

Fig. 6.—Tetralogy before and after valvotomy. Conversion of an extreme case of tetralogy into a mild case was forecast in the early postoperative period, because of the development of a loud, prolonged systolic murmur extending into, but not beyond, the aortic component, and the recording of a soft pulmonary component. A 2-year follow-up has confirmed this prediction.

One case is worth citing since it proved that excessive removal of the stenosis carries the hazard of converting Fallot's tetralogy to the situation of a large ventricular septal defect with large left-to-right shunt. This patient underwent a pulmonary valvotomy, with excellent result, the murmur becoming louder and longer, with disappearance of symptoms and cyanosis. However, 16 months later he developed bacterial endocarditis, during which pulmonary incompetence

emerged, suggesting that the pulmonary valve had been damaged. Following this illness, marked cardiomegaly developed and pulmonary plethora with "hilar dance" became a striking feature. There was now a very loud pansystolic murmur maximal in the pulmonary area, followed by a blowing diastolic murmur of pulmonary incompetence. Cardiac catheterization confirmed a gross left-to-right ventricular shunt of 7.9 liters per minute, pulmonary blood flow being 13.5 and systemic flow 5.6 liters per minute. Proximal right ventricular pressure was 130/10 mm. Hg, the systolic pressure being similar to aortic pressure (140/75 mm. Hg). Pressure in the outflow tract was 72/2, and in the pulmonary artery 35/10, mm. Hg. Pulmonary vascular resistance was low (0.3 units). At necropsy an unusually large septal defect (4 by 2 cm.) was found. There was no true infundibular stenosis and the pulmonary orifice admitted the index finger. The diameter of the pulmonary artery was nearly twice that of the aorta.

Comment: The findings show that this operation increases both pulmonary blood flow and length of the systolic murmur by reducing the severity of the stenosis. This proves the inverse relation between the length of murmur, which reflects the volume rate of blood flow through the stenosis, and the severity of the stenosis. The findings also indicate that auscultation provides an accurate indication at a very early stage of the likely result from this type of operation. The development of a loud systolic murmur extending into the aortic second sound, and a diminutive pulmonary second sound guarantees an excellent result, provided that relief of the stenosis has not been excessive. In fact, if a loud pansystolic murmur is heard over the right ventricle immediately after completion of the operation, it at once indicates that adequate relief of the stenosis has been produced. Wood[17] found that the murmur often became explosive after the Brock operation.

Auscultation proved superior to other methods in the early prediction of the result, since the improvement in pulmonary blood flow was promptly revealed by the change in the murmur, whereas radiologic methods required many months to demonstrate the change. Although lessening of the cyanosis was quite quickly shown, time was needed to evaluate the result on this criterion alone. Regression of clubbing took many months, and improvement in effort tolerance could only be assessed after full convalescence. The electrocardiogram was little value, since right ventricular hypertrophy persisted whatever the result.

2. *Blalock-Taussig Operation.*—To obtain further proof that the length of the systolic murmur is dependent on the severity of the stenosis, the effect of a Blalock-Taussig operation on the murmur was studied. The operation was performed in 7 cases, and in all but 1 the left subclavian artery was anastomosed to the pulmonary artery. In no case was a valvotomy or resection performed during the period of study, so that the operation achieved its effects quite independently of the stenosis. The result of operation, as determined by the same criteria used for the direct operation, was compared with auscultatory and phonocardiographic findings. Of the 7 cases, the result was bad in 1, slight in 1, good in 3, and excellent in 2. No correlation could be found between the length of the systolic murmur and the surgical result (Fig. 9, third row). Moreover, there was no

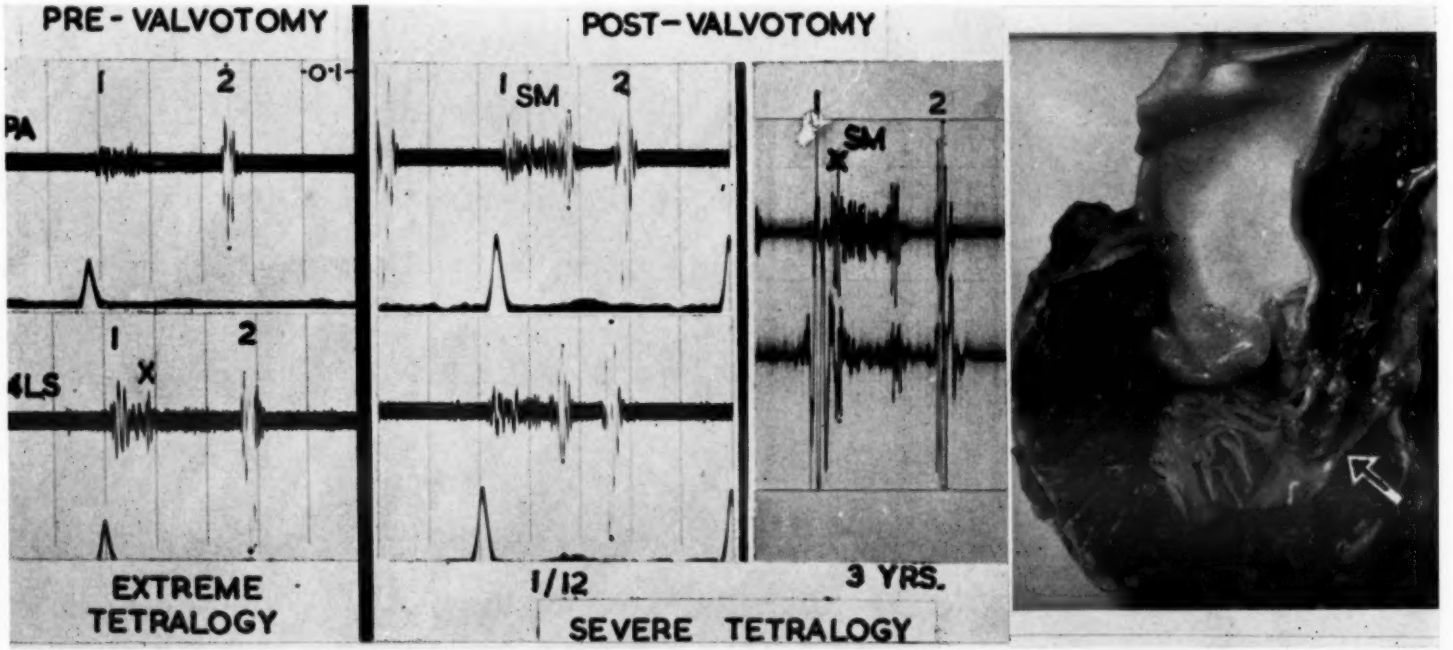

Fig. 7.—Tetralogy before and after valvotomy. Before operation the auscultatory features were those of extreme tetralogy. A bad result was predicted in the early postoperative period, because the murmur was that of severe tetralogy; moreover, it ended abruptly in midsystole, suggesting occlusion of the outflow tract during contraction of the infundibulum. Three years later the auscultatory features were unchanged, with persistence of the aortic ejection sound (*X*). The prediction of severe tetralogy was confirmed at necropsy. The specimen shows severe unrelieved infundibular stenosis (*arrow*).

increase in the length of the murmur after surgery in those cases showing as good a functional result as obtainable by the Brock operation (Fig. 9, and compare Figs. 6 and 8). These observations thus indirectly confirm the view that the length of the murmur is a function of the degree of stenosis in the tetralogy, provided the systemic resistance remains constant.

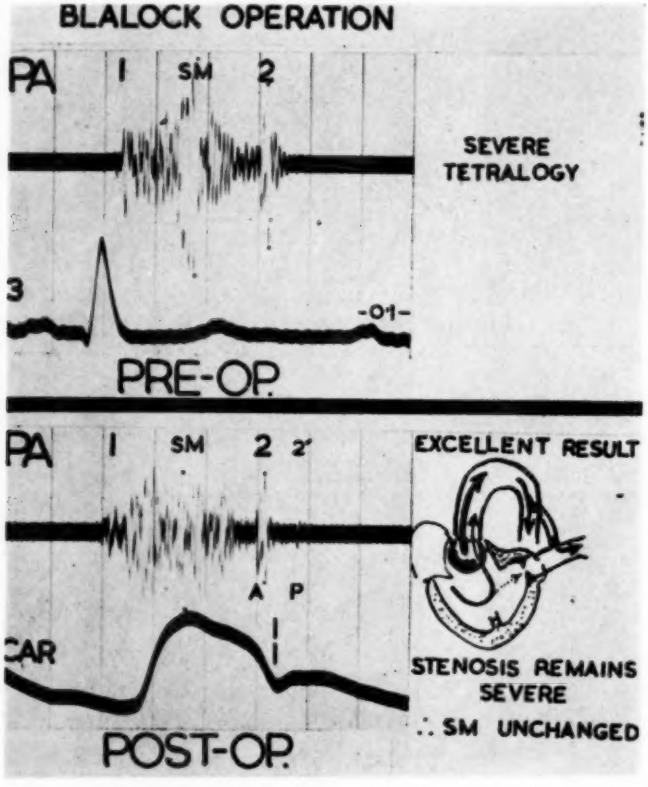

Fig. 8.—Fallot's tetralogy before and after a Blalock-Taussig operation. Although the result was excellent and associated with a loud continuous murmur and the emergence of a pulmonary component (*P*) suggesting a rise in pulmonary arterial pressure, the crescendo and duration of the systolic murmur remained unchanged because the stenosis had not been relieved.

Other auscultatory changes developed which were of value in predicting the result of this operation. A continuous murmur established the presence of a functioning anastomosis. This was always loud in good and excellent results. If, in addition to the continuous murmur, the pulmonary second sound, previously unrecordable, became recordable or even audible, it implied a significant rise in the pulmonary diastolic pressure[1,5] (Fig. 8). This occurred in 3 cases, all of which were considered to have had good or excellent results. Conversely, a very soft continuous murmur usually suggested an indifferent result, and the absence of a continuous murmur usually meant a nonfunctioning anastomosis, hence a bad result (Fig. 9).

3. *Complete Repair.*—Although the above-mentioned operative procedures are not ideal and will ultimately be replaced by the operation for complete repair

of the defects, they have been of great interest and value in supporting the thesis of this paper. Furthermore, the auscultatory signs described should continue to be of value where the facilities for complete repair are not available, or where a two-stage operation is planned. However, the ultimate objective must surely be repair of the septal defect and removal of the infundibular or valvular stenosis. Auscultation should also provide an early guide to the operative results, although the interpretation may be much more complex.

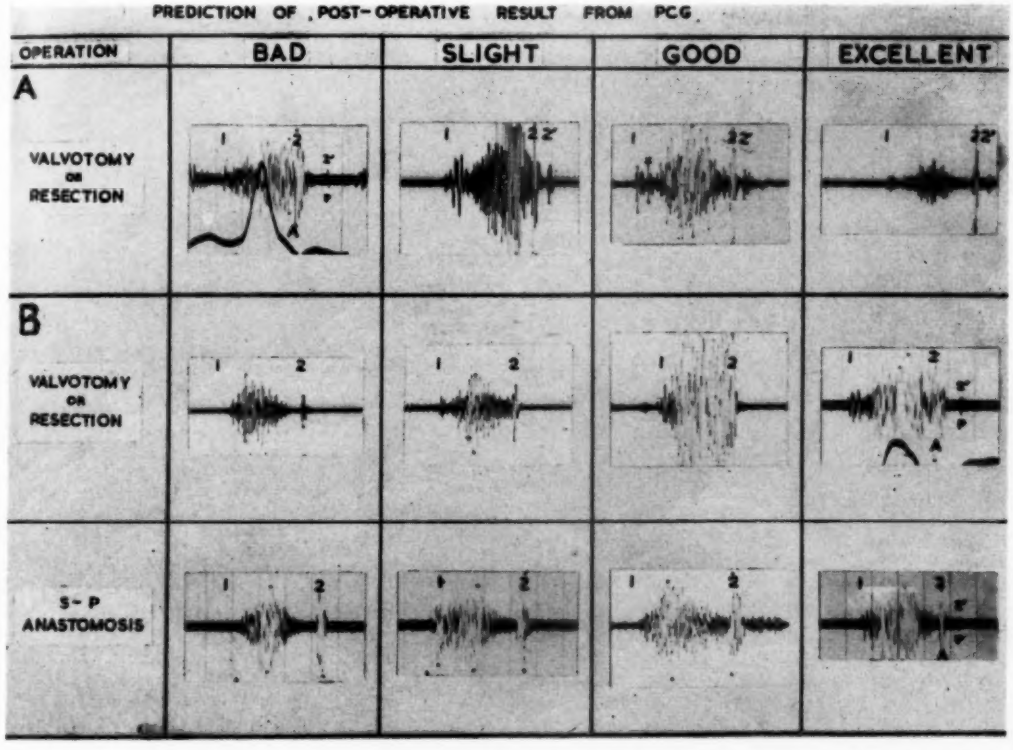

Fig. 9.—Prediction of the postoperative result from the phonocardiogram. See text for details. Note the opposite effect induced on the intensity and duration of the systolic murmur by a successful valvotomy or resection in cases of pulmonary stenosis and Fallot's tetralogy. A systemic-pulmonary anastomosis produced no lengthening of the pulmonary systolic murmur. *A*, Pulmonary or infundibular stenosis. *B*, Fallot's tetralogy.

Complete closure of the ventricular septal defect creates an intact ventricular septum. Any remaining infundibular or valvular stenosis will then exert an effect on the duration and height of right ventricular systole proportionate to its severity, as in stenosis with an intact ventricular septum. Thus, if the systolic murmur becomes or remains short, and narrow splitting develops, an excellent result can be predicted, since the short murmur reflects either mild residual stenosis or merely turbulent ejection of blood through a roughened outflow tract. Less adequate removal of the stenosis will result in a postoperative murmur of longer duration and wider splitting if a pulmonary component becomes recordable.

Incomplete closure of the ventricular septal defect with adequate relief of the stenosis will convert a large defect into a small one, and will introduce the pansystolic murmur of a ventricular septal defect with a small left-to-right shunt. Such a murmur should be readily distinguished from a prolonged murmur of moderate stenosis and intact septum by using amyl nitrite.[3,21] The murmur will soften in the former, and greatly increase in the latter, situation. Phenylephrine should also aid in diagnosis, since it causes pronounced intensification of the murmur of a septal defect but has very little effect in pulmonary stenosis with intact ventricular septum.[22,23] The use of amyl nitrite and phenylephrine should make it possible to determine the significance of a residual systolic murmur after the repair operation (see Fig. 5, Vogelpoel and associates[22]).

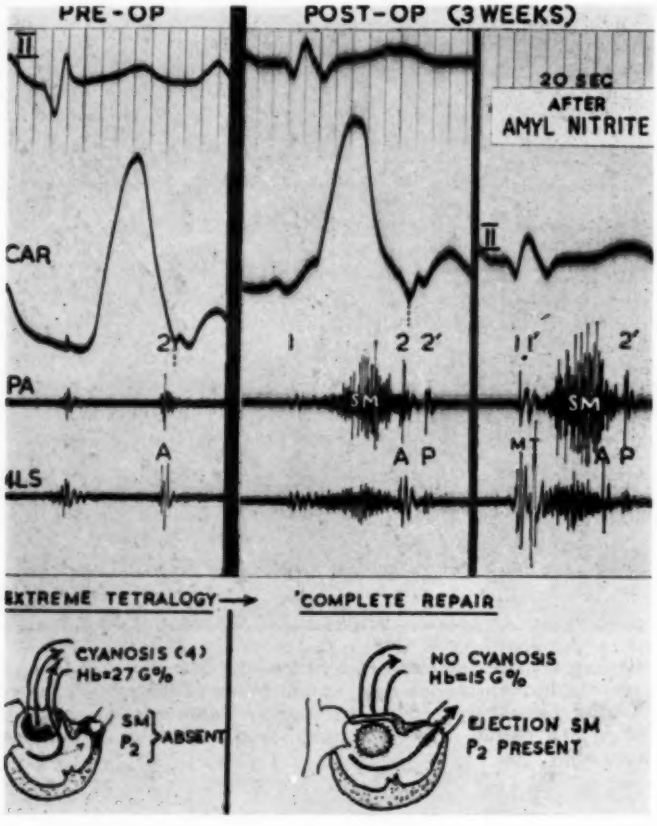

Fig. 10.—Tetralogy before and after complete repair. This was an extreme case in which a very soft, short, early murmur disappeared a few weeks before surgery. Severe infundibular stenosis was resected, and Ivalon patches were used to close the large septal defect and widen the outflow tract. Three weeks later a normal pulmonary component was recorded, denoting normal pulmonary arterial pressure and functioning of the pulmonary valve, no pulmonary incompetence, and a relatively short murmur. Amyl nitrite intensified the murmur, suggesting an ejection rather than a ventricular septal defect regurgitant murmur. Delay in the murmur and pulmonary second sound was due to complete right bundle branch block, shown also by split first sound after amyl nitrite.

The change in auscultatory features after complete repair was studied in 4 cases, 2 of which will be presented in detail, the first being an extremely severe case, and the second being a mild tetralogy. Fig. 10 illustrates the effect of com-

plete repair in the first case. The preoperative phonocardiogram revealed an extremely soft and short murmur confined to early systole, and absent pulmonary second sound. These features were those of extreme tetralogy, which was also shown by almost total disability and gross polycythemia. At operation a large septal defect was closed by a compressed Ivalon patch, and the severe infundibu-

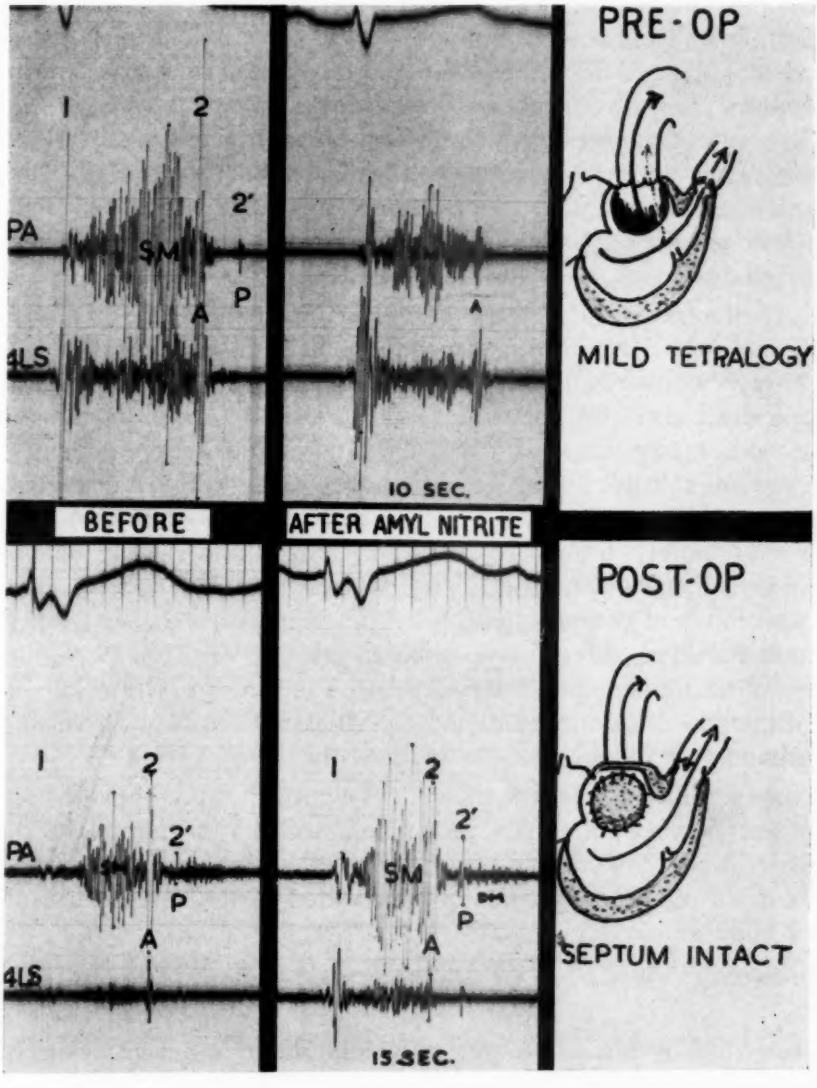

Fig. 11.—Mild tetralogy before and after complete repair. Before surgery, there was a loud murmur with late systolic crescendo and a widely split second sound due to a soft, audible, delayed (0.10 sec.) pulmonary component. Amyl nitrite softened the murmur and rendered P_2 inaudible, proving Fallot's tetralogy. At surgery, a large septal defect was found, together with relatively severe valvular stenosis (diameter of orifice, 4 mm.) and mild infundibular stenosis, illustrating that even in mild tetralogy the stenosis is severe. After valvotomy, infundibular resection, and closure of the septal defect, the murmur softened, but the configuration remained similar. However, amyl nitrite now intensified both murmur and pulmonary component, proving that the septum was intact. Note narrowing of split second sound to 0.06 sec. and pulmonary incompetent murmur (*DM*). Delay (shift to the right) in murmur and pulmonary component were presumably due to complete right bundle branch block, induced by surgery.

lar stenosis was resected and the outflow tract widened, using a patch in the ventricular wall. The right ventricular pressure dropped from 81/−4 to 52/5 mm. Hg, and the pulmonary arterial pressure rose from 22/15 to 47/12 mm. Hg. The postoperative result was excellent, with rapid disappearance of clubbing and symptoms. The phonocardiogram recorded 3 weeks after operation showed a loud, delayed pulmonary second sound and a late systolic murmur of short duration. Since the operation had induced complete right bundle branch block, the delay in the murmur and pulmonary component was attributed to delayed activation of right ventricular systole rather than to prolongation of systole from persisting severe stenosis. The intensification of the murmur after amyl nitrite indicated an ejection systolic murmur, rather than a murmur due to a small ventricular septal defect from incomplete closure of the defect. Furthermore, the increase was not so great nor so sustained as in cases of pulmonary stenosis,[3,21] so that the murmur was assumed to reflect turbulent flow through a roughened but not stenosed outflow tract.

Fig. 11 illustrates the effect of complete repair in a case of mild tetralogy. Following surgery, the murmur changed but little in configuration, but the response to amyl nitrite was quite different. Before surgery, the softening of murmur and disappearance of the pulmonary second sound proved tetralogy, whereas intensification of the postoperative murmur and pulmonary component confirmed that the septum had been rendered intact. The delay in murmur and pulmonary second sound (split was reduced from 0.10 to 0.06 second) was attributed to complete right bundle branch block rather than to any significant residual stenosis with intact septum. At operation, following complete valvotomy and infundibular resection and the use of an Ivalon patch to widen the outflow tract below the pulmonary valve, the right ventricular pressure dropped from 90/0 to 35/0 mm. Hg, and the pulmonary arterial pressure fell from 32/10 to 25/−1 mm. Hg, proving that the murmur could not be attributed to any significant stenosis. Mild pulmonary incompetence was induced by the operation.

In the remaining 2 cases, there developed midsystolic ejection systolic murmurs and normal pulmonary second sounds with moderately wide splitting after repair of the defects. However, considerable pulmonary incompetence in both, and tricuspid incompetence in one, added to the complexity of the postoperative findings.

SUMMARY

A study has been made to determine the value of auscultation and phonocardiography in assessing the result of surgery in cases of pulmonary stenosis with intact ventricular septum and Fallot's tetralogy.

In cases of pulmonary or infundibular stenosis with an intact ventricular septum, a successful valvotomy or infundibular resection resulted in marked shortening and softening of the murmur and reduction in the width of splitting of the second sound. Less adequate relief of stenosis caused less shortening of the murmur and less reduction in the splitting. Criteria are given for grading the postoperative severity of the stenosis.

In cases of Fallot's tetralogy, a successful valvotomy or infundibular resection (Brock operation) resulted in marked lengthening and intensification of the murmur and, frequently, the emergence of a very soft, audible pulmonary second sound widely separated (average 0.09 second) from the aortic second sound. These changes reflected increased volume rate of pulmonary flow through the stenosis and a rise in pulmonary arterial pressure. Less adequate relief of stenosis caused less prolongation of the murmur and no emergence of a pulmonary second sound. Criteria are given for grading the postoperative result.

Auscultation was shown to be an excellent bedside method of predicting the surgical result of a valvotomy in the two conditions, since the change in the length of the murmur and the width of splitting developed rapidly, and accurately reflected the degree to which the stenosis had been relieved. The opposite behavior of the murmur was due to the different dynamic situation in the two conditions. The observations proved that the length of the murmur was directly related to the severity of the stenosis when the ventricular septum was intact, but inversely related in cases of the tetralogy.

Following complete valvotomy under direct vision, the right ventricular pressure may fail to drop adequately because of severe subvalvular muscular hypertrophy. The resultant secondary infundibular stenosis may or may not regress over a period of time. The value of serial sound tracings in detecting the trend is emphasized. Gradual shortening of the initially prolonged murmur and narrowing of the split second sound indicate gradual reduction of right ventricular pressure and stenosis.

A successful Blalock-Taussig operation for the tetralogy did not lengthen the pulmonary systolic murmur, since the stenosis was not relieved by this operation. This indirectly confirmed the view that the length of the murmur is a function of the degree of stenosis, provided that the systemic resistance remains constant. However, auscultation was of value in other respects. The development of a loud continuous murmur, especially if associated with the emergence of a recordable pulmonary second sound, ensured a good result from this operation.

The use of auscultation in evaluating the result of the operation for complete repair of the septal defect and relief of the stenosis in cases of the tetralogy is discussed. The ideal end result is either a short ejection systolic murmur and narrow splitting of the second sound or no murmur at all, with normal heart sounds. The use of amyl-nitrite inhalation and phenylephrine in determining the origin of a residual systolic murmur is discussed.

We wish to thank members of the staff of Groote Schuur Hospital for referring cases for investigation, and the Superintendent, Dr. J. Burger, for his permission to publish our findings. We are indebted to Mr. Walter Phillips, Head of the Department of Thoracic Surgery, Mr. C. N. Barnard, full-time Senior Surgeon and Director of Surgical Research, Department of Surgery, University of Cape Town, and their surgical team for performing most of the operations and so successfully developing open-heart surgery. Without their skill and cooperation our observations could not have been made. We are particularly grateful to Dr. Maurice Nellen, Professor R. H. Goetz, and Dr. André Swanepoel for their assistance and cooperation. We gratefully acknowledge the great assistance received from our chief technician, Mr. L. W. Piller, as well as the help of Miss S. Joseph, Miss A. Ralston, Sister Key and Sister Abbott, and Mrs. C. M. Hall for typing and other services.

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The Electrocardiogram in Tetralogy of Fallot: A Study of 142 Cases

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There are many published reports on the electrocardiogram in cases of tetralogy of Fallot (TF). Some of the authors describe what they consider to be a very suggestive electrocardiographic pattern for this congenital defect.[1-4] Donzelot and associates[5] relate the electrical picture to such prevailing hemodynamic conditions as the balanced pressure between the right ventricle and the left ventricle. The overload of the right ventricle found in these circumstances is called by these authors an "adaptation overload." There are very few references to the vectorial analysis of the ECG in cases of this anomaly.[6]

Recently, several authors[7-10] have described a group of anomalies called "atypical Fallot," in which there is an interventricular septal defect (IVSD) associated with pulmonic stenosis, but in which a predominating arteriovenous shunt is found. In these cases, cyanosis is mild or absent and a clear enlargement of the left ventricle is seen and demonstrated by ECG and roentgenologic examination.

The scope of the present study is a vectorial analysis of the ECG in 142 cases of TF in order to determine: (1) what is the diagnostic value of a standard electrocardiographic pattern in TF; and (2) whether there is any difference between the electrocardiograms of the two main hemodynamic types of this malformation, one with right-to-left and the other with left-to-right shunt.

MATERIAL AND METHODS

Material.—A study was made on 142 cases of TF from the Hospital das Clínicas da Universidade de São Paulo, Hospital São Paulo da Escola Paulista de Medicina, and Santa Casa de Santos. Necropsy in 2 of these cases showed an interauricular septal defect (IASD), and in one other an anomalous pulmonary vein draining into the right auricle.

The diagnosis in each case was based on clinical and roentgenologic data, and was confirmed by angiocardiography in 120 cases. In 30 cases there was hemodynamic confirmation, and in 20

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cases a necroscopic study was made. The angiocardiographic diagnosis of tetralogy of Fallot was based upon the existence of pulmonic stenosis associated with an early filling of the aorta through the right ventricle. When the diagnosis was based on cardiac catheterization, there was evidence of a definite pressure gradient between the pulmonary artery and the right ventricle, as well as the passage of the catheter from the right ventricle into the aorta. Eighty-three of these patients were males and 59 were females. They ranged in age from 20 days to 29 years.

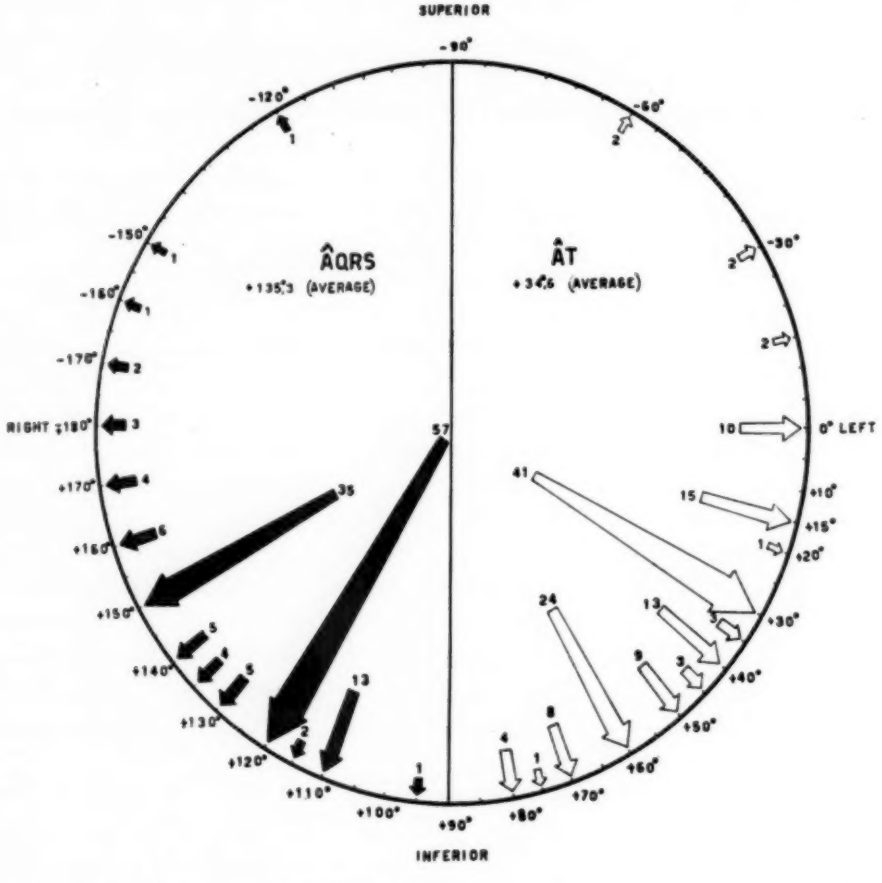

Fig. 1.—Orientation of the ventricular activation and repolarization vectors in the frontal plane. A study of 142 cases of tetralogy of Fallot.

Methods.—In the study of the P wave in 141 cases the role played by the heart rate was analyzed by dividing the patients into such age groups as would allow for the utilization of Ziegler's standards of normality.[11] Thus, in each age group the data were always obtained for two groups of patients, one with heart rate lower, and the other with heart rate higher, than the average considered normal for the respective age group.

The model described by Peñaloza and Tranchesi[12] was used for the determination of the SÂP, and the electrical center of the auricular activation process was considered to be projected anteriorly at the C_1 level.

For the vectorial analysis of the ventricular ECG, the leads were the standard bipolar leads I, II, III, the unipolar leads aVR, aVL, aVF, and the unipolar chest leads V_1 through V_6. The determination of the SÂQRS and SÂT vectors and the spatial angle between these two vectors was made using the previously described model.

The electrical center of the ventricular activation process was considered to be projected anteriorly at the level of C_1 instead of C_2, because in all cases there was a clear right ventricular hypertrophy which deviated the apparent center of origin of the vectors.

RESULTS

A. *Auricular Activation Process.*—The diagnosis of right auricular enlargement was made in 61 (43 per cent) cases, using the classic criteria based mainly on the voltage of the P wave.

1. *Amplitude of the P wave:* In only 7 out of 141 cases was the amplitude of the P wave in the right chest leads, mainly in Lead V_1, higher than that found in the classic leads. The chief factors which influenced the height of the P wave are discussed in the following paragraphs.

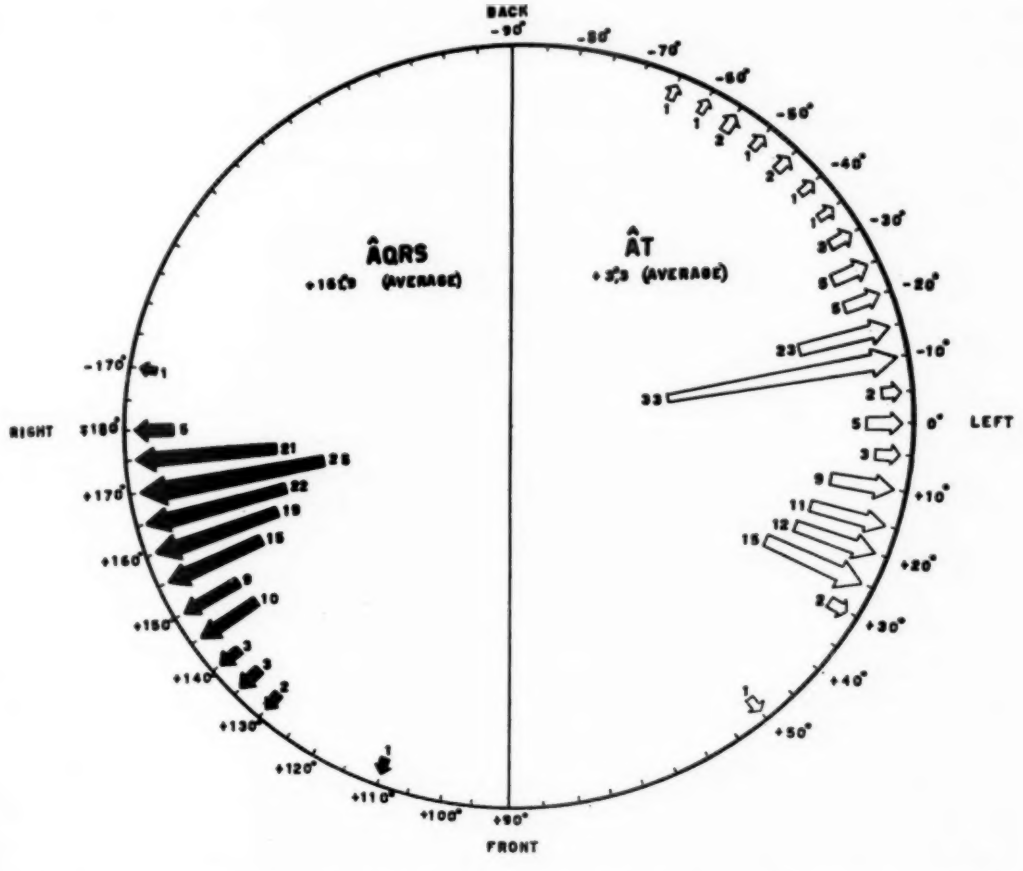

Fig. 2.—Orientation of the ventricular activation and repolarization vectors in the horizontal plane. A study of 142 cases of tetralogy of Fallot.

a. The influence of the heart rate was very clear in all age groups. Considering separately the two groups, one with rate below and the other with rate above the normal average, the following mean values (in mm.) were obtained: 1.89 and 2.58 (under 1 year of age), 2.44 and 2.59 (2 to 3 years), 1.95 and 2.44 (4 to 5 years), 2.48 and 2.75 (6 to 8 years), 2.58 and 2.86 (9 to 12 years), and 2.25 and 2.85 (over 13 years).

Regarding the incidence of pathologic deviation, P waves higher than maximal normal values were obtained in the same two aforementioned groups: respectively, in 22.2 and 60.0 per cent (under 1 year), in 38.1 and 41.7 per cent

(2 to 3 years), in 18.2 and 46.2 per cent (4 to 5 years), in 33.3 and 50.0 per cent (6 to 8 years), in 50.0 and 71.4 per cent (9 to 12 years), and in 20.0 and 63.2 per cent (over 13 years of age).

b. The relationship between the degree of desaturation of the arterial blood and the amplitude of the P wave was studied in 27 cases in which there was a clear tendency toward the appearance of high P waves while the O_2 saturation decreased. Thus, out of 13 patients with a P wave measuring 3 mm. or more, 12 showed a saturation of less than 75 per cent and 1 showed a saturation of 76.9 per cent. The maximal amplitude (5.2 mm.) was obtained in a patient with 67 per cent saturation, and the greatest desaturation (22 per cent) was found in a patient with a P wave 4 mm. in height.

Significative correlation ($P = 0.10$, critical level = 0.05) between the considered parameters was not observed; there was clear dispersion of the P-wave amplitude values in cases with marked arterial desaturation. For instance, a P wave with small amplitude (1.5 mm.) was found in a patient with a saturation of 59.7 per cent.

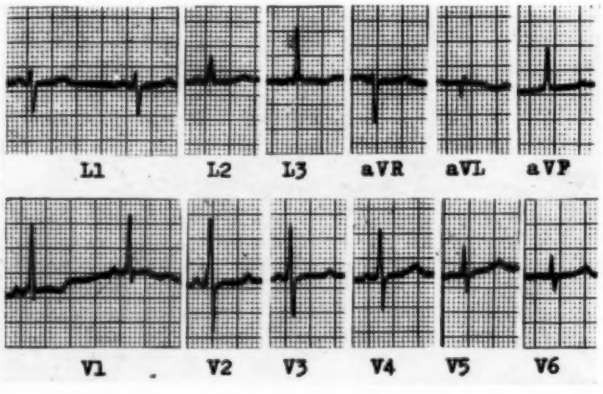

Fig. 3.—Typical electrocardiogram in tetralogy of Fallot (11-year-old girl). Complexes of the Rs type with initial slurring in Lead V_1 and positive T waves from Leads V_2 to V_6.

2. *Duration of the P wave:* Duration of the P wave was influenced slightly by the age factor, oscillating between 0.05 and 0.08 second among patients under 9 years of age. A duration of 0.09 second was found only in patients who were 10 years of age or over.

3. *The SÂP axis:* The SÂP axis ranged from +30° to +75° in 133 cases, and was usually directed forward (in 128 cases). A more leftward position was observed in 6 patients, being around 0° in one of them. In the other 2 cases, the SÂP was directed a little more rightward (between +80° and +85°). Exceptionally, the SÂP was oriented backward (in 8 cases) or parallel to the frontal plane (in 5 cases).

4. *Ventricular complexes of the qR pattern:* Such complexes were observed in Lead V_1 in 5 cases, and 4 of the them showed roentgenologic signs of marked right auricular enlargement. Two of these patients showed an accentuated enlargement (+++) of the right auricle at necropsy, and one of these showed a pulmonary vein draining anomalously into the right auricle.

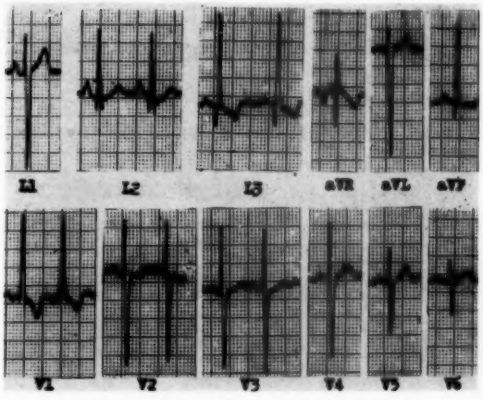

Fig. 4.—Tetralogy of Fallot (5-year-old boy). Note the rsR′ morphology in Lead V_1.

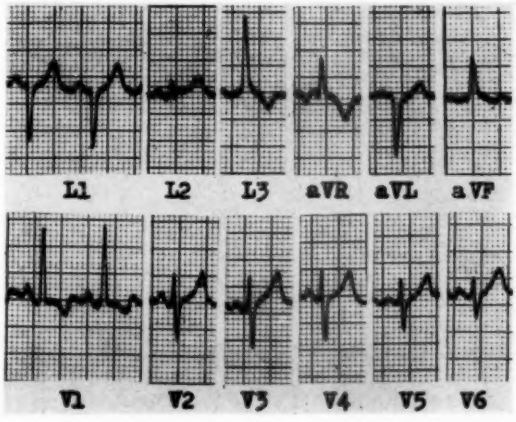

Fig. 5.—Tetralogy of Fallot (4-year-old girl). Note the "pure" R morphology in Lead V_1.

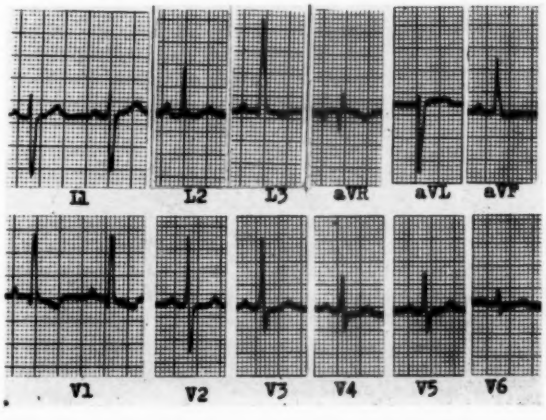

Fig. 6.—Tetralogy of Fallot (14-year-old girl). Observe the qR morphology in Lead V_1. Necroscopy revealed marked enlargement of the right auricle.

TABLE I

PATIENT NUMBER	AGE	HEART RATE (PER MINUTE)	$\hat{A}$QRS (DEGREES)	QRS IN V_5, V_6	INTRINSICOID DEFLECTION	LEFT VENTRICLE (X-RAY)	CYANOSIS
1.	13 yr.	115	+ 110	qRs	0.039	+	—
2.	19 yr.	88	+ 120	qRs	0.038	—	+++
3.	18 mo.	130	+ 150	qRs	0.039	+ Necropsy	—
4.	3 yr.	105	+ 110	qRs	0.020	—	++
5.	5 mo.	160	+ 110	qRs	0.038	+	+ On effort
6.	2 yr.	136	+ 120	qRs	0.032	—	+++
7.	1 yr.	160	+ 140	qRs	0.028	—	++
8.	4 yr.	105	+ 120	qRs	0.036	—	+++
9.	4 yr.	120	+ 120	qRs	0.040	+	+
10.	6 yr.	100	+ 120	qRs	0.032	—	+++
11.	5 yr.	120	+ 120	qRs	0.030	—	+++
12.	17 yr.	100	± 180	qRs	0.040	+	+ On effort
13.	2 yr.	110	+ 120	qRs	0.034	—	+++
14.	14 mo.	150	+ 95	qR	0.038	+ Necropsy	+
15.	4 yr.	75	+ 120	qR	0.040	+	+ On effort
16.	29 yr.	75	+ 115	qRs	0.042	+	+
17.	7 yr.	100	+ 130	qRs	0.034	—	+
18.	8 yr.	100	+ 110	qRs	0.040	?	+
19.	5 yr.	110	+ 110	qRs	0.040	+	+
20.	15 yr.	75	+ 120	qRs	0.042	+	+ On effort
21.	3 yr.	110	+ 140	qRs	0.035	—	+++
22.	2 yr.	120	+ 140	qRs	0.032	?	+++
23.	5 yr.	115	+ 120	qRs	0.034	?	+
24.	8 yr.	75	+ 120	qRs	0.036	—	+++
25.	11 yr.	115	+ 120	qRs	0.035	—	+++
26.	10 yr.	75	+ 120	qRS	0.040	+	+ On effort
27.	10 yr.	125	+ 140	qRS	0.039	+ Necropsy	+
28.	19 yr.	90	+ 120	qRS	?	—	+++
29.	18 yr.	73	+ 130	qrS	?	—	+++
30.	3 yr.	110	+ 150	qRS	0.028	—	+++
31.	6½ yr.	100	+ 150	qrS	?	—	+++
32.	6 yr.	100	+ 135	qRS	0.030	—	+++
33.	25 yr.	68	+ 150	qRS	0.030	—	++
34.	4 yr.	75	+ 120	qRS	0.036	—	++

TABLE II. T WAVE IN PRECORDIAL LEADS

	LEAD	CASES	PER CENT
Negative	in V_1	55	38
	in V_1 and V_2	19	13.3
	in V_1, V_2, and V_3	8	5.6
	from V_1 to V_6	3	2.1
Positive	from V_1 to V_6	53	37
	in V_1 and negative or "infantile" type in V_5-V_6	3	2.1

B. *Ventricular Activation Process.*—

1. *Orientation of the SÂQRS (Figs. 1 and 2):* In all cases the SÂQRS was directed rightward and predominantly forward and downward. It was directed upward in 5 cases, and backward only in 1 case showing predominantly negative QRS complexes in Lead V_1. The projection of the SÂQRS in the frontal plane

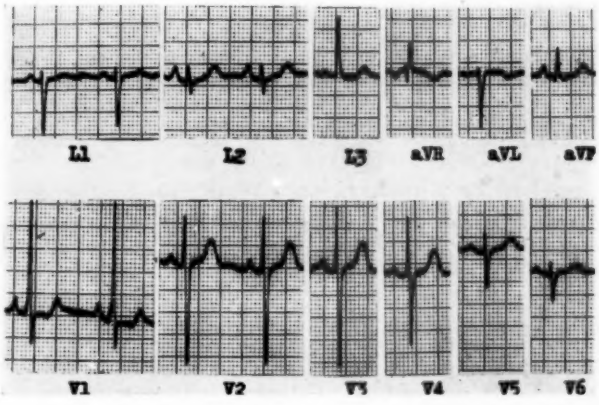

Fig. 7.—Tetralogy of Fallot (6-year-old girl). Complexes of the Rs type with initial slurring in Lead V_1 and qrS in Leads L1 and V_6.

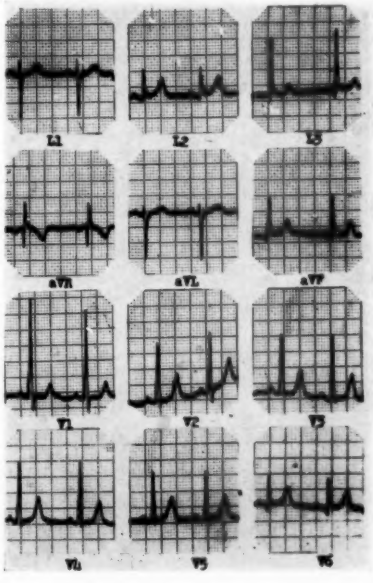

Fig. 8.—"Atypical Fallot" (4-year-old boy). Electrocardiographic signs of combined ventricular overloading. Note the qR morphology in Lead V_6 with intrinsicoid deflection measuring 0.042 second.

was between +95° and −120°, predominantly between +120° and +150° in 106 cases (74 per cent), the mean value being +135.3° (Fig. 1). In the horizontal plane the most frequent projection of SÂQRS was between +145° and ±180° in 132 cases (92 per cent), the mean value being +161.9° (Fig. 2).

2. *Morphology of QRS complex in Lead V_1:* There was a great preponderance of the Rs pattern with an initial thickening of the ascending limb of R (Fig. 3) in Lead V_1, in 88 cases (62 per cent). In 22 cases (15.5 per cent) an rsR′ pattern was found (Fig. 4). In 9 cases (6.5 per cent) a mere positive deflection of the R type with an initial thickening was observed. The R pattern without an initial thickening (7 cases or 4.9 per cent) (Fig. 5) and a qR pattern (5 cases or 3.5 per cent) (Fig. 6) were very rare. In 11 cases (7.5 per cent) the rS or RS pattern was registered from Leads V_1 to V_6.

3. *Comparative study of the QRS complex in Leads V_1 and V_2:* In 68 cases (48 per cent) there was a transition from an essentially positive QRS complex (Rs) in Lead V_1 to an essentially negative complex (rS) in Lead V_2 (Fig. 7). In 74 cases (52 per cent) there was no abrupt transition, but progressive diminution of the R wave from Leads V_1 to V_4 and predominantly positive complexes (Rs or RS with R larger than S) were registered in Lead V_2 (Figs. 3 and 6).

4. *Morphology of QRS complex in Leads V_5 and V_6:* The Q wave was not registered in Leads V_5 and V_6 in 108 cases (76 per cent); among these, 68 cases (48 per cent) had an rS pattern and 40 cases (28 per cent) had an RS pattern. In the other 34 cases (24 per cent) a Q wave was registered and the ventricular complexes had the qRs (16 per cent), qRS (4 per cent), qrS (2 per cent) (Fig. 7), and qR (1.5 per cent) (Fig. 8) patterns. These cases were studied particularly for the purpose of finding a correlation among these patterns, the intrinsicoid deflection in Leads V_5 and V_6, the size of the left ventricle in the roentgenologic examination, and the degree of cyanosis (Table I).

Upon roentgenologic examination it was found that in 13 cases there was an enlargement of the left ventricle; in 3 of them this was confirmed at necropsy. In all cases the intrinsicoid deflection was delayed and cyanosis was mild or present only on effort. Left ventricular enlargement was confirmed in 2 cases with a qR pattern in Leads V_5 and V_6. In all of the cases with a qrS pattern the left ventricle was of normal size.

C. *Ventricular Recovery Process.*—

1. *Orientation of the $\hat{S}\hat{A}T$ (Figs. 1 and 2):* The vector that represents ventricular repolarization was directed leftward in all cases. In 136 cases (96 per cent) it was directed downward, and in 80 cases (56 per cent) it was directed backward. The ÂT ranged from $-60°$ to $+80°$ in the frontal plane, chiefly between $+30°$ and $+60°$ (43 cases or 30 per cent), the mean value being $+34.6°$. In only 4 cases was the ÂT found between $-30°$ and $-60°$. In the horizontal plane, the ÂT ranged from $-65°$ to $+50°$, chiefly between $-30°$ and $+30°$ (128 cases or 90 per cent), the mean value being $+3.3°$.

2. *Polarity of the T wave in precordial leads:* T-wave polarity in precordial leads is summarized in Table II. The ventricular repolarization wave was positive in all of the precordial leads in 53 cases (37 per cent) (Fig. 7), and negative (asymmetric with relatively low voltage) from Leads V_1 to V_6 in only 3 cases (2.1 per cent). In 3 other cases the T wave was positive in Lead V_1 and negative or of the "infantile" pattern in Leads V_5 and V_6; these patterns have already been described by Zuckermann and associates[13] in cases of transposition of the great vessels.

D. *Spatial Angle Between the Vectors of Ventricular Activation and Repolarization (SÂQRS-SÂT Angle).*—The mean value of the SÂQRS-SÂT angle was 99.51°. In the frontal plane the opposition between the ÂQRS and ÂT vectors was moderate, the angle between the two being around 100°. In the horizontal plane this opposition was greater, the mean value of the angle being 158.6°.

DISCUSSION

A. *Auricular Activation Process.*—The study of the auricular complex confirmed the absence of very high amplitudes of the P wave; on the basis of this finding, there was relatively low incidence of the diagnosis of right auricular overload. This is in contrast to what is observed in cases of pure pulmonic stenosis or pulmonic stenosis associated with IASD.[14-17]

The height of the P wave can be influenced not only by right auricular enlargement but also by the heart rate and, in a less important way, by the degree of peripheral oxygen desaturation, the effect of which could possibly be related to the increased tonus of the sympathetic systems.[18] We emphasize that in 7 cases the auricular complex showed a normal voltage in the classic leads and a much increased voltage in the right precordial leads, mainly in Lead V_1. This finding could be partly explained by the tendency of the auricular electrical field forces to be perpendicular to the frontal plane leads, and by the fact that sometimes, due to great enlargement of the right chambers, Lead V_1, by its proximity, can be considered a semidirect lead.

In 133 cases (94 per cent) the SÂP axis was located between +30° and +75°, being directed forward in 128 cases. This latter fact may be related to the relative preponderance of the right auricular forces.

In 5 cases a qR pattern in Lead V_1 (Fig. 6), according to the criteria of Sodi-Pallares and associates,[19] gave the clue to the diagnosis of right auricular enlargement. Upon roentgenologic examination, 4 of these cases presented a marked right auricular dilatation, and this fact was confirmed by necropsy in 2 cases. The significance of this pattern will be discussed later in this paper.

B. *Ventricular Activation and Recovery Processes.*—

1. *Sequence of activation spread:* On the basis of the study of direct epicardial leads in TF carried out by Barbato and associates,[20,21] we can conclude that the trabecular zone and the surrounding paraseptal areas are the earliest to be activated. The next area to be activated is the so-called intermediate zone of the right ventricle; activation here probably occurs simultaneously, at least partially so, with the activation of the free wall of the left ventricle. The pulmonary conus is activated last. Although exploration of the crista supraventricularis and the posterobasal zones of the right ventricle was not possible, we assume that they are activated at a later stage than the pulmonary conus.

These data allow us to present the sequence of the ventricular activation spread in cases of TF in the following way: The beginning of the activation process can be represented by a vector directed forward, rightward, and more often downward than upward; this corresponds to the preponderance at this moment of the activation process of the middle third of the left septal mass, trabecular

zone of the right ventricle, and paraseptal zones. Immediately after this, during the left ventricular activation process a second vector directed to the free wall of this chamber is observed. Generally, this vector has little magnitude because it is soon dominated by important opposing electrical forces (third vector) oriented forward, rightward, and downward and related to the hypertrophied right ventricular mass. Those electrical forces represent the activation spread of the intermediate zone and of the pulmonary conus. At last, during the activation process of the basal portions of the septum and of the right ventricle (including the crista supraventricularis), electrical forces appear which can be represented by a fourth vector oriented upward, backward, and to the right.

In the tetralogy of Fallot the frequent preponderance of the third vector is one of the main causes that favor the rightward, forward, and downward orientation of the SÂQRS.

In rare cases in which an rS pattern is observed from Leads V_1 to V_6 (only 1 case in our material), we can assume that the electrical field during the ventricular activation process was oriented upward, backward, and to the right, on account of a great preponderance of the fourth vector. In these cases, essentially positive QRS complexes are registered in the posterobasal zones of the right ventricle (by means of direct epicardial leads) and in the right-superior area of the chest (by means of the conventional ECG).

2. *Morphology of the QRS in Lead V_1:* Our results concerning the morphology of QRS complexes in Lead V_1 agree with those of many other authors,[1-5] and the most frequent morphology was the Rs pattern with an initial thickening. "Pure" R and qR patterns in Lead V_1 are very rare in TF, whereas rsR′ and RS patterns are a little more frequent (Figs. 3-6).

Direct epicardial leads obtained from patients with TF[22] showed that the aforementioned patterns are found in different areas of the right ventricle. Thus, Rs (with initial thickening) and rsR′ patterns are registered mainly in the pulmonary conus. RS patterns are obtained in the right paraseptal zones and in the intermediate zone, and rS patterns are obtained in the trabecular zones.

The several patterns in right ventricular overloading keep a certain correspondence with the relation between the systolic pressures of the right and left ventricles.[22] Thus, the Rs patterns (with an initial thickening) are very frequent in conditions in which the right and left ventricles have similar systolic pressures, regardless of the nature of the cardiopathy. It is generally known that in TF the pressures in the two ventricles are very similar, and this was confirmed in 30 of our cases submitted to cardiac catheterization. This fact may partially explain the high incidence of the Rs (62 per cent of the cases). We wish to emphasize that in 53.3 per cent of our cases of pure pulmonic stenosis with similar pressures in the right and left ventricles, Rs patterns (with an initial thickening) were registered in Lead V_1.[22]

The rsR′ pattern with normal duration of the QRS complex in Lead V_1 was found in 15.5 per cent of our cases. According to our experience, this pattern is more often related to heart diseases in which the right ventricle has lower systolic pressures than does the left, as for instance in IASD or in pulmonic stenosis. The finding of this pattern in Lead V_1 in cases of TF allows us to assume that

other factors besides the hemodynamic overload interfere in its electrogenesis. By means of direct epicardial leads obtained in cases of TF with an rsR′ pattern in Lead V_1[20] a definite lag of the activation spread in the pulmonary conus was demonstrated. For this reason, we assume that besides the ventricular overload there must be some important disturbance in the intraventricular conduction in these cases.

In only 5 cases was the qR pattern obtained in Lead V_1; this pattern is found more frequently in heart diseases in which the systolic pressure is higher in the right than in the left ventricle. These patients showed a marked cardiomegaly, a rare occurence in this congenital defect, and 4 of them showed a definite dilatation of the right auricle. In 2 of these cases, necropsy was performed, demonstrating in one an associated IASD and in the other one an anomalous pulmonary vein draining into the right auricle. These data permit us to suggest the possibility of the existence of an abnormally dilated right auricle associated with a cardiomegaly whenever a qR pattern in Lead V_1 is obtained in cases of TF.

3. *Comparative study of the morphology of QRS complex in Leads V_1 and V_2:* When Donzelot and associates[5] established the concept of an "adaptation overload" of the right ventricle, taking as an example cases of TF, they assumed that in these instances, contrary to the "barrier overload" observed in cases of pure pulmonic stenosis, the transition of QRS from Leads V_1 to V_2 was abrupt, jumping from a predominantly positive complex (Rs) to an essentially negative one (rS). Our results, like those obtained by Espino Vela and co-workers,[23] do not confirm this fact; occurrence of abrupt transition (48 per cent) was about as frequent as the so-called "slow transition" (52 per cent) from Leads V_1 to V_2.

4. *Morphology of QRS in Leads V_5 and V_6:* Seventy-six per cent of our cases showed in the left precordial leads, rS and RS patterns related to a great overload of the right ventricle.

In 24 per cent of the cases, a Q wave was registered in Leads V_5 and V_6, with the following patterns (in order of frequency): qRs, qRS, qrS, and qR. These patterns in the presence of definite signs of right ventricular overload often suggest an associated enlargement of the left ventricle. However, we know that many cases of pure pulmonic and mitral stenosis with a Q wave in the left precordial leads associated with an Rs or "pure" R pattern in Lead V_1 showed no left ventricular enlargement at necropsy.

In the diagnosis of left ventricular overload associated with TF, we consider as valuable data a delayed intrinsicoid deflection and the presence of a qR pattern in Leads V_5 and V_6 (Table I; Fig. 8).

Among the causes of left ventricular enlargement in cases of TF are: increase of the collateral circulation, arteriovenous shunt due to IVSD, and associated ductus arteriosus. In our material, in spite of the surgeon's report of definite collateral circulation in 42 cases, no signs of left ventricular overload were observed upon roentgenologic or ECG examination. Thirteen of the cases studied presented left ventricular enlargement, but increase of the collateral circulation was not observed in these cases.

We assume that the foregoing examples, on account of their clinical (relatively slight cyanosis) and roentgenologic (normal or slightly increased pul-

monary circulation) features, can be classified as cases of the so-called "atypical Fallot" with preponderance of arteriovenous shunt through the IVSD.

5. *Ventricular recovery process:* In the majority of cases of TF, the SÂT is oriented downward, backward, and to the left; this is in accordance with the behavior of the ventricular recovery in right ventricular overload: namely, the SÂT opposing the SÂQRS. The opposition of these two vectors is more marked in the horizontal plane (mean value of 158.6°) than in the frontal plane (mean value of 100°); this fact may be related to the peculiar spatial orientation of the SÂT and SÂQRS in patients with TF.

Although the value of the SÂT-SÂQRS angle is increased in TF, this increase is not excessive as it is in cases of extreme right ventricular overload. In these cases, chiefly those of pure pulmonic stenosis, as the pressure in the right ventricle surpasses that in the left, the SÂT is directed upward and more backward, and a negative T wave appears in Lead aVF, Lead II, and many precordial leads.

The great frequency of a positive T wave from Leads V_1 to V_6 or from Leads V_2 to V_6 must be related to the type of right ventricular overload found in TF, in which the balanced pressures in both ventricles do not favor the backward and upward deviation of the SÂT.

The morphology of the T wave in the chest leads is also closely related to the above-mentioned hemodynamic conditions.[5,24] When a negative T wave is registered in a right precordial lead, it is of small amplitude and has the tendency to be asymmetric and to present a terminal positivity. This morphology of the T wave is in clear contrast to that found in cases of extreme right ventricular overload in which the T waves are negative, peaked, and of high voltage, associated with marked depression of the RS-T junction.

In 2 of our cases presenting a negative T wave from Leads V_1 to V_6, one had anatomic confirmation of diffuse myocarditis, and the other, because of great cardiomegaly, had a clinical diagnosis of associated myocardial disease.

C. *Electrocardiographic Patterns in Tetralogy of Fallot.*—An analysis of our material enables us to conclude that in the majority of cases of TF the ECG tracing tends to have a uniform behavior which allows us to describe an electrocardiographic pattern found in this type of congenital heart disease (Fig. 3). Thus: (1) The SÂQRS is directed rightward, downward, and forward, with the ÂQRS situated predominantly between +120° and +159°. (2) The SÂT is directed downward, leftward, and backward, with ÂT usually between +30° and +60°. (3) There is an Rs pattern with an initial thickening of R in Lead V_1 and rS or RS pattern in Leads V_5 and V_6. (4) A positive T wave appears in all of the precordial leads, or only a negative and asymmetric T wave with low voltage is seen in Lead V_1 or in Leads V_1 and V_2.

In our opinion, this combination of electrocardiographic signs is not diagnostic of TF but can be found in any cardiopathy with similar pressure conditions in the two ventricles. These electrocardiographic features represent, therefore, the pattern of heart disease with the so-called "systemic right ventricle."

In the presence of a cyanotic congenital heart disease with this electrocardiographic standard, the diagnosis of TF is very likely, not only because this mal-

formation is the most frequent among the cyanotic congenital malformations of the heart, but also because of the fact that the equality of pressures between the two ventricles is the rule in this cardiopathy.

When in a case of TF a qR, qRs, or qRS pattern with a delayed intrinsicoid deflection is registered in Leads V_5 and V_6, we can diagnose an associated left ventricular enlargement which might be related to an arteriovenous shunt through the IVSD, if less probable conditions like a persistent ductus arteriosus or increased collateral circulation are absent.

In a very small number of cases, the SÂQRS is directed upward, rightward, and backward, and rS or RS (with predominant negative phase) patterns are registered in all the precordial leads. In these cases, the ECG is very similar to that found in cases of single ventricle.

SUMMARY

One hundred and forty-two cases of tetralogy of Fallot were studied from both the scalar and the vectorial electrocardiographic points of view.

We have concluded that in the majority of the cases of this congenital heart disease the ECG shows a uniform behavior which relates to the hemodynamic picture. We have established the criteria for the diagnosis of the left ventricular enlargement which may eventually co-exist, indicating a predominant left-to-right shunt through the interventricular septal defect (atypical Fallot).

Finally, we have emphasized the presence of qR patterns in the right precordial leads in cases of TF associated with marked cardiomegaly and evident enlargement of the right auricle.

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Chronic Pernicious Myocarditis

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Fiedler,[1] in 1899, described four cases of acute interstitial myocarditis with autopsy findings. These cases constituted a heterogeneous group morphologically as well as clinically. Two were of the interstitial type, one should be classed as giant cell myocarditis, and one seems to have been caused by a virus.[2] Yet it is undoubtedly to Fiedler's credit that he directed attention to a clinical entity, a disease localized to the myocardium, and affecting mainly the younger age group. The onset of this illness is often sudden, with chills, fever, and precordial pain. Difficulties in breathing, rapid pulse rate, and cardiac dilatation with tachycardia quickly develop, and the patients usually die within one or several weeks after the onset of the disease. The sudden onset and the fulminating course are quite characteristic. Schmorl, who studied the microscopic sections of the heart of these patients, stressed the absence of any changes in the endocardium and pericardium, the "isolated" involvement of the myocardium, and the interstitial nature of the myocarditis, with an infiltration of lymphocytes, histiocytes, a few plasma cells, polymorphonuclear leukocytes, and occasional myogenic giant cells. He emphasized the interstitial location of the exudate but also mentioned various degenerative changes of the muscle fibers.

A number of subsequent studies confirmed the existence of acute isolated myocarditis, which now is a well-recognized clinical entity with nonspecific ECG abnormalities.[3] Anatomically, the changes are not specific and there is no one predominant type of cell. The interstitial nature of the myocardial exudate is usually stressed. Thus, it should be emphasized that Fiedler originally, and a number of other investigators subsequently, described an acute form of myocarditis, of sudden onset and with a quickly developing fatal course. However, in later years, the term "Fiedler's myocarditis" was also applied to a type of myocarditis anatomically similarly isolated, and inevitably causing death with myocardial failure, but in a patient who gradually developed symptoms with a protracted downhill course. The course of this type of myocarditis may last a few months or several years. As compared with the acute form of myocarditis, which Fiedler had described and which rapidly leads to final myocardial failure,

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the long-lasting, chronic form of isolated myocarditis may be a separate entity, different in its onset, course, and anatomic picture. Since the cause of neither of these two entities, the acute and chronic, is known, it is possible that the chronic form of isolated myocarditis constitutes either a continuation of the acute stage of the disease, or is an a priori different entity.

It is the purpose of this study to stress the chronic form of isolated myocarditis which, because of its relentless course ending in severe myocardial failure, may be termed "pernicious myocarditis," in accordance with Boikan's designation.[4]

Kelle,[5] in 1892, was apparently the first to direct attention to a truly chronic form of myocarditis in contradistinction to myocardial fibrosis due to coronary artery disease. Some of the cases he referred to were obviously rheumatic in type or occurred following contagious diseases such as scarlet fever, typhoid fever, or diphtheria. Other cases, however, did not disclose any anamnestic data of a disease which might be associated with myocarditis. Kelle stressed that these chronic myocarditides are found especially in patients who are less than 40 years old, that the heart is always enlarged, and that on occasion a diastolic or a presystolic murmur over the apex of the heart may be elicited which simulates that occurring in stenosis of the mitral orifice. Microscopically, progressive myocardial fibrosis was described, together with round cell infiltrations, eventually culminating in severe interstitial fibrosis.

Boikan,[4] working in J. Erdheim's laboratory, reviewed the literature up to 1931. He described a 28-year-old woman who had several attacks of pharyngitis. Four months before death she developed cyanosis, anasarca, high pulse frequency with gallop rhythm and dilatation of the heart. The myocardial failure grew relentlessly worse. At autopsy, outspoken chronic myocarditis was found, with foci of interstitial fibrosis. Boikan described the myocarditis as principally and primarily interstitial in nature, with secondary connective tissue replacement of some of the muscle fibers. There was no evidence of primary muscle damage such as that occurring in diphtheria. The valvular apparatus, mural endocardium, and the pericardium were free from changes. The simultaneous findings of more acute changes and fibrotic regions were emphasized and taken as evidence of the true chronic nature of the myocarditis, which had its clinical counterpart in the progressive downhill course of the disease and the invariable fatal ending.

To underline the so characteristic downhill course and the pessimistic outcome of this disease, Boikan recommended the term "pernicious myocarditis."

The purpose of this communication is to stress the occurrence of a pernicious type of myocarditis as visualized by Boikan and to show that anatomically "pernicious" myocarditis is not just *one* entity, but that the various myocarditides may run a clinical course similar to Boikan's pernicious myocarditis. Futhermore, it is intended to show that among all types of myocarditides, a chronic form of *isolated* myocarditis is in our geographic region the most common anatomic finding in cases which clinically appear to be of the pernicious variety.

LITERATURE

We have attempted to collect from the literature those cases which, in retrospect, may be classified as cases of pernicious myocarditis. The pertinent data are summarized in Table I. Besides the cases listed in Table I there exists another type of chronic myocarditis which obviously belongs to the group of pernicious myocarditis. This type is that occurring in Chagas' disease. Such cases have been observed for many years in South America, particularly in Venezuela, Brazil, and Argentina, ever since 1928, when Chagas[18] described severe heart involvement in the disease which carries his name. More recently, Laranja and associates[19] (1956), in a clinical, epidemiologic, and pathologic study, again pointed to the common myocardial involvement in this disease. Although the acute form of myocarditis may lead to a rather quickly ensuing death with evidence of circulatory failure, the chronic myocarditis following the so-called asymptomatic period is more important. Laranja and associates remarked that in an unselected population from 5 to 60 years of age, 32.7 per cent of the people with chronic *Trypanosoma cruzi* infection had chronic heart damage. They stressed that progressive heart involvement with a prolonged chronic course is characteristic. Irregularities of cardiac rhythm, gallop rhythm, and systolic murmurs due to functional mitral or tricuspid regurgitation may be present, and electrocardiographic abnormalities were extremely common. The relentless downhill course despite all known therapy is often significant. The chief anatomic findings in the 21 cases reported by these authors included hypertrophy of the heart, enlargement of all cardiac cavities, a marked inflammatory process of the myocardium with diffuse fibrosis and infiltration by lymphocytes, macrophages and plasma cells, and, in some cases, eosinophils and polymorphonuclear leukocytes. The leishmanial forms of *Trypanosoma cruzi* were present in all of their 21 cases. Laranja and associates significantly remarked that in countries in which Chagas' disease exists in an endemic form, such diagnoses as Fiedler's myocarditis, chronic myocarditis of unknown etiology, or myocardial disease of unknown cause should not be made unless Chagas' disease has been adequately excluded as a possible etiological factor.

Very recently, also, Funes[20] (1958) stressed the chronicity of myocarditis in Chagas' disease and the very unfavorable prognosis.

From the foregoing it is clear that in countries in which Chagas' disease is endemic a chronic form of myocarditis occurs which clinically is often of the pernicious type in the sense discussed above.

From the short review of the literature it is perfectly clear that a chronic type of myocarditis exists, pernicious in character and lasting several months or longer. The relentlessly downhill course of this protracted heart disease, with remissions and exacerbations unavoidably causing death, is characteristic clinically. Anatomically, the most common findings in the heart are consistent with a chronic isolated type of myocarditis.

Our interest in this subject was aroused by a recent case of obvious pernicious myocarditis which came under our observation. Stimulated by this finding, we examined the files of our more recent autopsy cases, omitting autopsies on

TABLE I. DATA ON CASES OF CHRONIC PERNICIOUS MYOCARDITIS*

AUTHOR AND DATE	AGE OF PATIENT (YR.)	SEX OF PATIENT	DURATION OF DISEASE	PROGRESSIVE MYOCARDIAL FAILURE	TYPE OF DEATH	CLINICAL NOTES
Boikan[4] (1931)	28	F	4 mo.	+	Unexpected	Gallop rhythm
Simon and Wolpaw[7] (1935)	23	M	5½ wk.	+	Unexpected	Systolic murmur at apex, tachycardia
Lindberg[6] (1938)	11	M	8½ mo.	+	Unexpected	History of whooping cough
Smith and Stephens[8] (1938)	38	F	Several mo.	+	Unexpected	Tachycardia
	38	F	13 mo.	+	Unexpected	Tachycardia
	43	M	2 yr.	+	Gradual	Gallop rhythm
	38	F	28 mo.	+	Gradual	Gallop rhythm; cardiac invalid for 2 yr.
Smith and Furth[9] (1943)	40	M	3 yr.	+	Unexpected	Systolic murmur at apex, auricular fibrillation, ventricular premature contractions
	35	M	9½ mo.	+	Unexpected	Tachycardia. Alterations in the T waves and R-T segments
	35	F	8 yr.	+	Unexpected	Systolic murmur at apex, intraventricular heart block, and ventricular premature contractions
Moe and LeMar[10] (1948)	68	M	18 mo.	+	Gradual	Systolic murmur

Griffith and Herman[17] (1952)	37	F	12 mo.	+	Unexpected	Myocardial failure following diphtheria; systolic murmur at apex, arrhythmias
Blanshard[11] (1953)	20	M	6 mo.	+	Gradual	Gallop rhythm, systolic murmur
Guistra[16] (1954)	8	M	3 yr.	+	Gradual	Myocardial failure following measles; bizarre arrhythmias and conduction block
Antes[12] (1955)	19	M	19 mo.	+	Gradual	Gallop rhythm
Balchum, et al.[13] (1956)	38	F	2 yr.	+	Unexpected	Low voltage T-wave changes, gallop rhythm, systolic murmur at apex
Lichtenberger[14] (1957)	38	M	5 mo.	+	Unexpected	Cough, dyspnea, jaundice, malaria
(Only 6 of his 9 cases seem to belong to this entity)	38	F	18 mo.	+	Unexpected	Right bundle branch block, ventricular premature contractions
	48	M	4 mo	+	Unexpected	Systolic murmur at apex, ventricular premature contractions, tachycardia
	48	M	7 mo	+	Unexpected	Ventricular premature contractions, 2:1 A-V block
	26	M	15 mo.	+	Unexpected	Weak heart sounds, died following pericardiotomy (*Necator americanus* infestation)
	37	M	5 wk.	+	Unexpected	Weak heart sounds, tachycardia
Kavelman[15] (1958)	38	M	12 mo.	+	Gradual	Gallop rhythm, systolic murmur at apex, ventricular premature contractions, tachycardia

***A number of the older cases could not be used because of incomplete histories. For available data on these, see Scott, R. W., and Saphir, O.: Acute Isolated Myocarditis, Am. Heart J. 5:129, 1929.**

the newborn and infants. Our material comprised 2,652 autopsies. Among these 2,652 autopsies, 225 cases of myocarditis were encountered. This is a percentage of 8.4. The relatively high percentage of cases is probably the result of routine scrutinization of many blocks of the myocardium microscopically. Among these 225 cases of myocarditis, 6 were reclassified as chronic pernicious myocarditis. These 6 cases form the basis of the present study. Only the most important clinical and pathologic findings will be given.

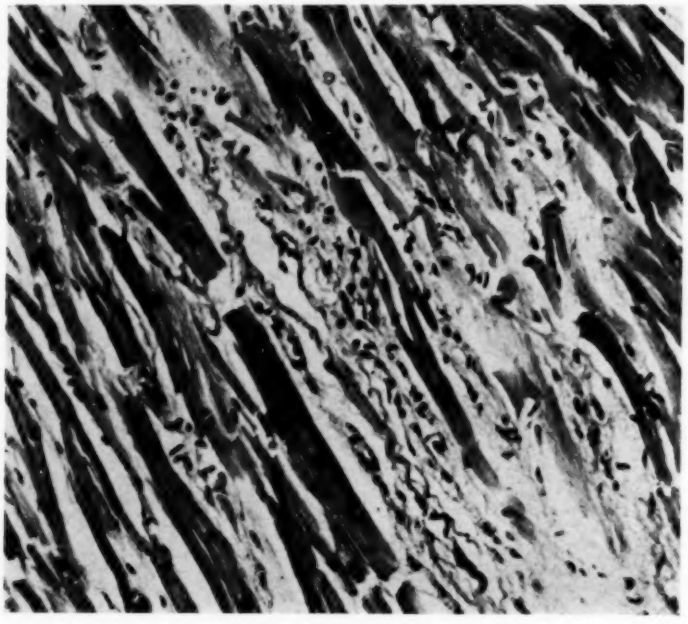

Fig. 1.—Case 1. Note the interstitial infiltration of lymphocytes and the spreading apart of muscle fibers by young connective tissue fibers. (Hematoxylin and eosin preparation, ×150).

CASE REPORTS

CASE 1. *Clinical Findings.*—A 24-year-old Negro woman was well until 6 months prior to admission, when she developed fatigue, had dyspnea on exertion, and began to cough up whitish sputum. The shortness of breath continued relentlessly until she developed "three pillow" orthopnea. Edema of the lower extremities began 2 months later. She was hospitalized and digitalized 3 months before death. There was no previous history of rheumatic fever. On admission she had a pulse rate of 126 per minute and an arterial blood pressure of 150/105 mm. Hg. The temperature was 100.4°F. The heart was enlarged and there was a Grade 1 systolic murmur at the apex. The liver was enlarged and there was bilateral ankle and pedal edema. An electrocardiogram* showed nonspecific changes, modified later by digitalis. She also had a 4+ albuminuria. She expired suddenly 4 days after admission.

Autopsy Findings.—There was an excessive amount of clear fluid in both pleural cavities and within the peritoneal cavity. There was chronic passive hyperemia of the liver and spleen. The heart was hypertrophic and dilated, weighing 460 grams. The epicardium was smooth and shiny. All of the chambers of the heart were equally dilated. The mural endocardium and the valvular apparatus were intact. The coronary arteries were normal. The myocardium was firm and had a normal architecture.

***We are indebted to Dr. Alfred Pick, Physician-in-Charge, Heart Station, Michael Reese Hospital, for the interpretation of the electrocardiograms of all of our cases.**

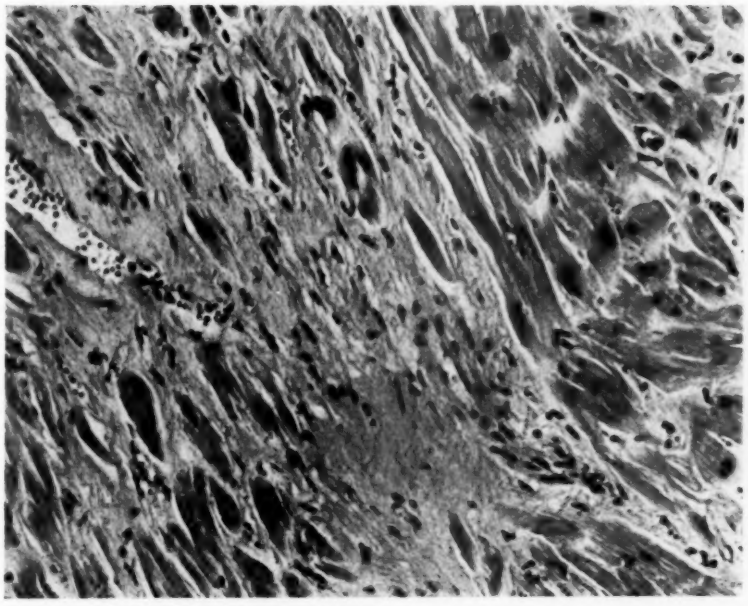

Fig. 2.—Case 2. Note the interstitial fibrosis with a number of spindle-shaped fibroblasts and a few lymphocytes. Muscle fibers are markedly compressed and atrophic. (Hematoxylin and eosin preparation, ×150).

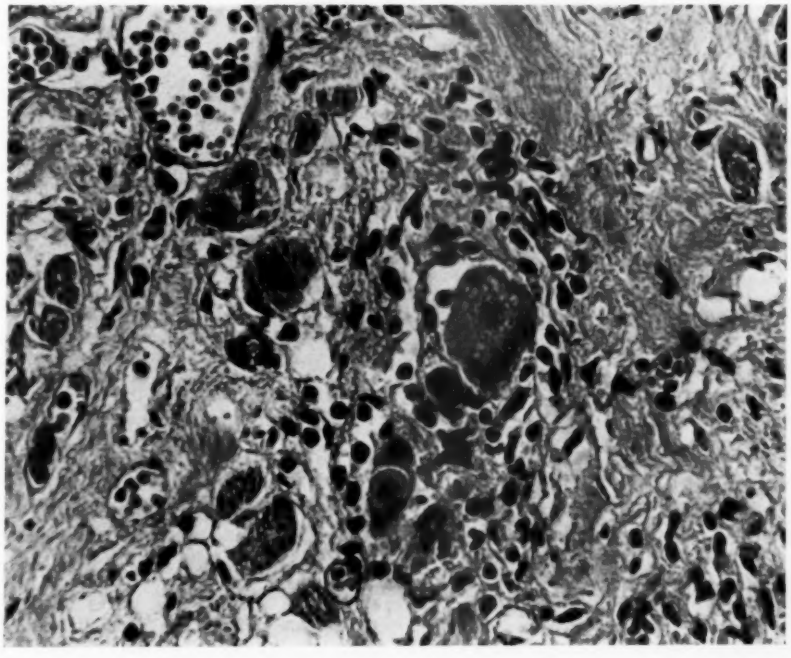

Fig. 3.—Case 2. Note the fibrous replacement of heart muscle fibers, some of which are broken up and show degenerative changes. There are also inflammatory cells, mainly lymphocytes. Some heart muscle nuclei appear large and hyperchromatic. (Hematoxylin and eosin preparation, ×375).

Sections of the myocardium disclosed a new formation of connective tissue interrupting the course of the heart muscle fibers and often, also, following the course of the fibers. Varying numbers of lymphocytes and a few histiocytes were noted in these areas. In some fields there was a moderate amount of edema-like material adjacent to muscle fibers. In isolated areas, small accumulations of lymphocytes and histiocytes were observed in the absence of newly formed connective tissue. The muscle fibers themselves were relatively large, and some of them were fragmented. The outstanding change was the marked, mainly interstitial, fibrosis. (See Fig. 1.)

Summary.—A 24-year-old woman gradually developed evidence of myocardial failure. There was no history of a preceding illness. After a relentless downhill course she expired suddenly a little over 6 months after the onset of the disease. Autopsy disclosed a dilated and hypertrophied heart with diffuse chronic interstitial myocarditis.

CASE 2. *Clinical Findings.*—A 50-year-old white woman had a long history of heart disease, supposedly of rheumatic origin but without a history of rheumatic fever. She was digitalized 6 years before death and was in congestive failure for 4 years. Clinically, she had mitral stenosis, tricuspid insufficiency, hypertrophy of the heart, and congestive failure. Her temperature was normal. There was a rumbling mid-diastolic murmur at the apex and auricular flutter. Her pulse rate was 140 per minute. The electrocardiograms showed a persistent RBBB with frequent attacks of atrial flutter or fibrillation. During sinus rhythm there were varying degrees of A-V block. Because of the clinical impression of severe mitral stenosis a mitral commissurotomy was performed. At surgery, a seeming stenosis was felt in the region of the mitral valve, but direct left atrial and ventricular pressure recordings did not reveal a marked gradient across the mitral valve. Ventricular contractions were poor. Postoperatively, she went into shock and expired 2 days later.

Autopsy Findings.—There was chronic passive hyperemia of the lungs and liver. Sanguinous fluid was found within the left pleural cavity. The heart weighed 400 grams, and the epicardium was smooth and shiny. The right atrium and both ventricles were moderately dilated. The mural endocardium and the valvular apparatus were intact. There was no anatomic evidence of stenosis of the mitral orifice. The coronary arteries disclosed only slight arteriosclerotic changes. The myocardium was pale, gray, and rather firm.

Microscopic examination of the myocardium revealed relatively large muscle fibers with various degrees of degenerative changes. There was marked new formation in connective tissue, which separated bundles of muscle fibers from one another. Often, too, individual muscle fibers were separated from one another by old hyalinized connective tissue. In other fields there was a moderate amount of lymphocytes and histiocytes infiltrating perivascular spaces and the newly formed connective tissue between muscle fibers. In several areas, large accumulations of lymphocytes were noted between muscle fibers, and in others, cellular connective tissue fibers were present with a few newly formed, small-sized blood vessels. The outstanding changes in the myocardium were foci of chronic inflammation with lymphocytes and histiocytes and a new formation of young connective tissue fibers rich in cellular elements. Common, too, was old hyalinized connective tissue, diffusely distributed throughout many sections and replacing heart muscle fibers. Rarely, a few giant cells were seen which were of the myogenic type, with cytoplasm identical to that of muscle fibers. These giant cells were considered to be abortive attempts at muscle fiber regeneration. (See Figs. 2 and 3.)

Summary.—A 50-year-old woman showed characteristic findings of mitral stenosis. She was in congestive failure several times. A commissurotomy was eventually contemplated. At operation, no definite evidence of stenosis of the mitral orifice was encountered. She died 2 days after the operation. Autopsy disclosed a large heart without valvular deformity. On microscopic examination there was a diffuse, chronic myocarditis.

CASE 3. *Clinical Findings.*—A 48-year-old white man had severe mental depression and a history of alcoholism for 2 years. Three weeks prior to his admission he was treated for "heart trouble." At that time he had dyspnea and ankle edema. On admission he looked chronically ill and had a pulse rate of 150 per minute with gallop rhythm. His temperature was 101.2°. No murmurs were audible. The heart was slightly enlarged, and an electrocardiogram showed left heart strain with progressive reduction of voltage. Terminally, paroxysmal congestive failure ensued. He expired suddenly 2 weeks after admission.

Autopsy Findings.—There were 500 c.c. of amber fluid in the peritoneal cavity, and 150 c.c. in each pleural cavity. There was chronic passive hyperemia of the liver, lungs, spleen, and kidneys, and multiple pulmonary emboli were found. The heart weighed 600 grams, and the myocardium was softer than normal. The right atrium was markedly dilated, and the right auricular appendage contained small, adherent thrombi. The subepicardial fat tissue was abundant and appeared to infiltrate into the right ventricular wall. The left ventricle was markedly dilated and hypertrophied. The valvular apparatus was normal.

Sections of the myocardium disclosed a marked new formation in connective tissue, principally along the course of heart muscle fibers. Lymphocytes, fibroblasts, and histiocytes were often found interspersed between newly formed connective tissue fibers. Hyalinization of connective tissue was commonly observed in perivascular areas. In other sections there were accumulations of lymphocytes and myocardial reticulocytes perivascularly and extending into the interstitial tissue spaces between the course of muscle fibers. In a number of fields the myocardium could be compared with a sieve, the myocardial fibers corresponding to the holes of the sieve, and the connective tissue fibers forming the framework of the sieve itself. (See Fig. 4.)

Summary.—A 48-year-old man had been ill at least 5 weeks with gradually increasing congestive failure. He succumbed suddenly. Autopsy disclosed a large, dilated heart, the seat of a marked chronic diffuse myocarditis.

Fig. 4.—Case 3. Note the spindle-shaped cells and connective tissue fibers between the muscle fibers. There are also a few lymphocytes. (Hematoxylin and eosin preparation, ×375).

CASE 4. *Clinical Findings.*—An 8½-year-old Negro girl had a history of pertussis at age 6, and since then she tired easily and had dyspnea on exertion. Five days prior to admission she developed severe orthopnea. On admission she had a pulse rate of 134 per minute, her temperature was 100.4°, and she had signs of left ventricular failure. There was a systolic gallop rhythm at the tricuspid area. The electrocardiogram showed changing nonspecific alterations, at times with a pattern of left heart strain and multifocal (atrial, A-V nodal, and ventricular) premature systoles. She was digitalized, with good results. In the following 2 months she decompensated twice, requiring redigitalization. During the next 4 weeks she again developed evidence of uncontrollable myocardial failure, and expired 4 months after admission.

Autopsy Findings.—There was marked pitting edema of both lower extremities, and chronic passive hyperemia of the lungs and liver. There was a large amount of clear fluid within the serous

cavities. The heart was markedly dilated and hypertrophic, weighing 380 grams. There was a small, slightly adherent mural thrombus in the right auricular appendage. The valvular apparatus was intact. The myocardium of both the right and left ventricles was soft, pale, and flabby. The septum of the left ventricle showed streaks of subendocardial fibrosis.

Sections of the myocardium showed a number of areas in which the muscle fibers were spread apart, either by a new formation in connective tissue which was rich in cellular elements, or by an edema-like material. In only a very few regions were the muscle fibers actually interrupted by connective tissue. Most commonly, the connective tissue fibers extended parallel to the course of muscle fibers. The perivascular spaces were greatly increased. Often, individual muscle fibers were flanked on both sides by connective tissue. A moderate number of inflammatory cells, mainly lymphocytes and histiocytes, were found between muscle elements.

Summary.—An 8½-year-old girl developed congestive failure following an attack of pertussis. She had a relentlessly downhill course and died 4 months after admission, 2½ years after onset of the disease. At autopsy there was a large, flabby heart, and sections disclosed chronic myocarditis, with relatively few inflammatory cells but with a marked new formation of connective tissue fibers.

CASE 5. *Clinical Findings.*—A 20-year-old white woman was first seen at Michael Reese Hospital 16 months prior to death, with the complaints of dyspnea on exertion and angina. Twelve months previously she had had hepatitis. On admission she had an enlarged heart, and there was a soft basal systolic murmur and, after exercise, a diastolic rumble. Her temperature was normal, and there was a pulse rate of 130 per minute. The arterial blood pressure was 112/74 mm. Hg. The electrocardiogram showed large, bizarre P waves and nonspecific ST-T abnormalities. Because of cardiac catheterization findings corroborating the clinical observations, a diagnosis of mitral stenosis was made. The patient was maintained on digitalis and was seen 4 months later, when she was 7 months pregnant. After a normal delivery she was discharged in good compensation. She was found dead 9 months later.

Autopsy Findings.—There was chronic passive hyperemia of the lungs, liver, spleen, and kidneys. The heart weighed 390 grams and was markedly dilated. The endocardium was smooth throughout, and the valvular apparatus was intact. The left ventricle was hypertrophied, measuring 2.1 cm. in thickness. Sections through the myocardium revealed a brownish-red, firm tissue with normal architectural markings.

Microscopic sections of the myocardium disclosed a new formation of connective tissue fibers separating bundles of muscles and individual muscle fibers from one another. In some fields it seemed as though the entire myocardium were furrowed through with connective tissue fibers. A number of connective tissue fibers were still cellular, and only a few fibers appeared to be hyalinized. In other sections the newly formed connective tissue also disclosed varying numbers of histiocytes, lymphocytes, and myocardial reticulocytes. In other fields there were a few capillaries within the connective tissue fibers. Surrounding the capillaries an edema-like material was present, further spreading already compressed muscle fibers. (See Figs. 5 and 6.)

Summary.—This 20-year-old woman had evidence of congestive failure which was thought to have been caused by mitral stenosis. She had several remissions and survived a full-term pregnancy. Some time later she suddenly expired. Autopsy disclosed an enlarged heart with chronic diffuse interstitial myocarditis.

CASE 6.* *Clinical Findings.*—A 43-year-old white woman was in good health until 10 months prior to death. Progressive dyspnea and swelling of the lower extremities developed. Six months later she had an acute febrile illness, with an increase in dyspnea and edema. She was discharged from another hospital with the diagnosis of cardiac failure and pneumonitis. She continued to have a downhill course, despite digitalis and mercurial diuretics. She was admitted to this hospital in severe congestive failure, with marked pitting edema and diffuse râles over the chest. There was a Grade 3 systolic murmur at the apex, and the pulse rate was 120 per minute. The temperature was 101°F. Her arterial blood pressure was 130/78 mm. Hg. The electrocardiogram showed, at first, sinus rhythm with alterations suggesting hypokalemia, and then, atrial fibrillation with runs of bidirectional ventricular tachycardia. The pericardium was explored but no changes were found. She expired several hours postoperatively.

*This case will be reported in greater detail by Drs. E. N. Silber, A. Schaffer, and A. Cahue.

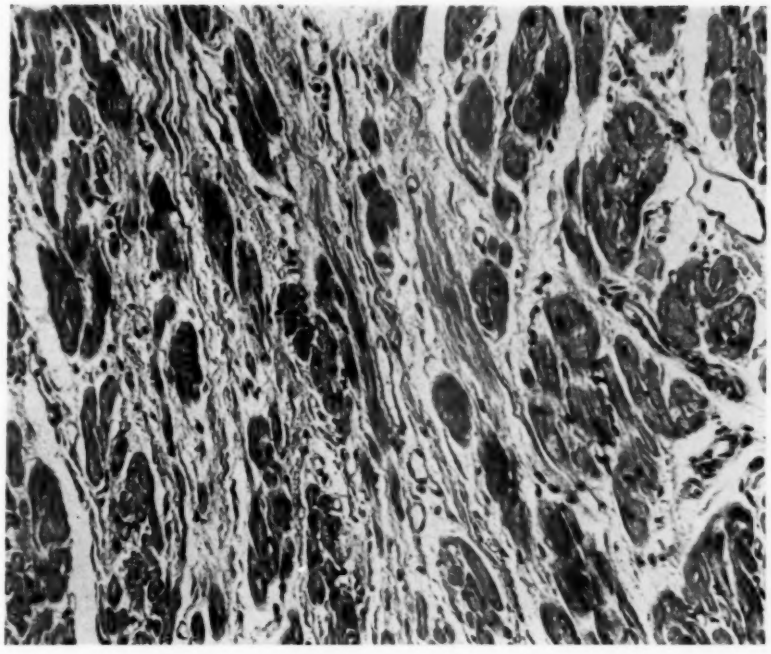

Fig. 5.—Case 5. Note the marked interstitial fibrosis with only a few spindle-shaped nuclei and a few lymphocytes. (Hematoxylin and eosin preparation, ×150).

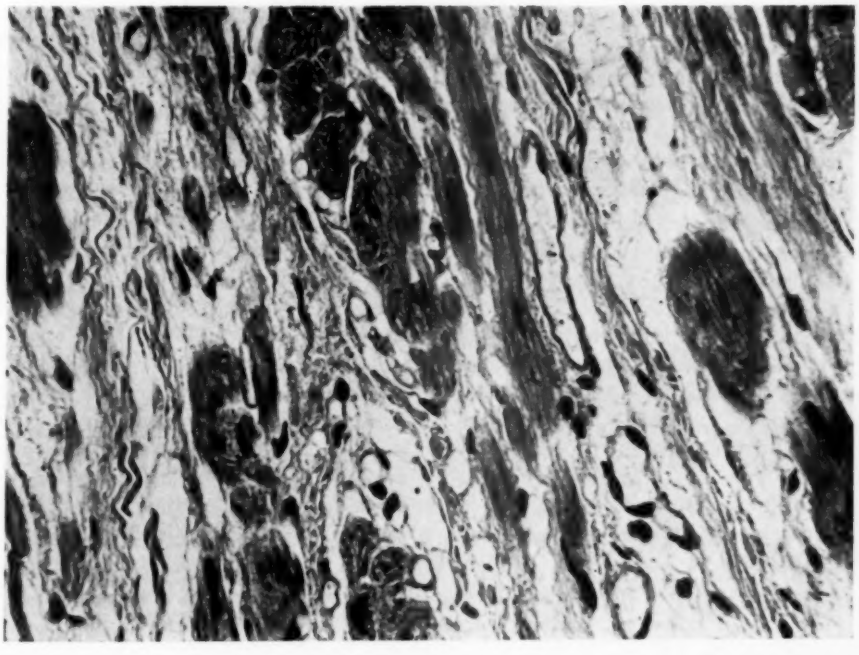

Fig. 6.—Case 5. A higher magnification of Fig. 5. Note the severe interstitial fibrosis with broken up muscle fibers and a few inflammatory cells. (Hematoxylin and eosin preparation, ×375).

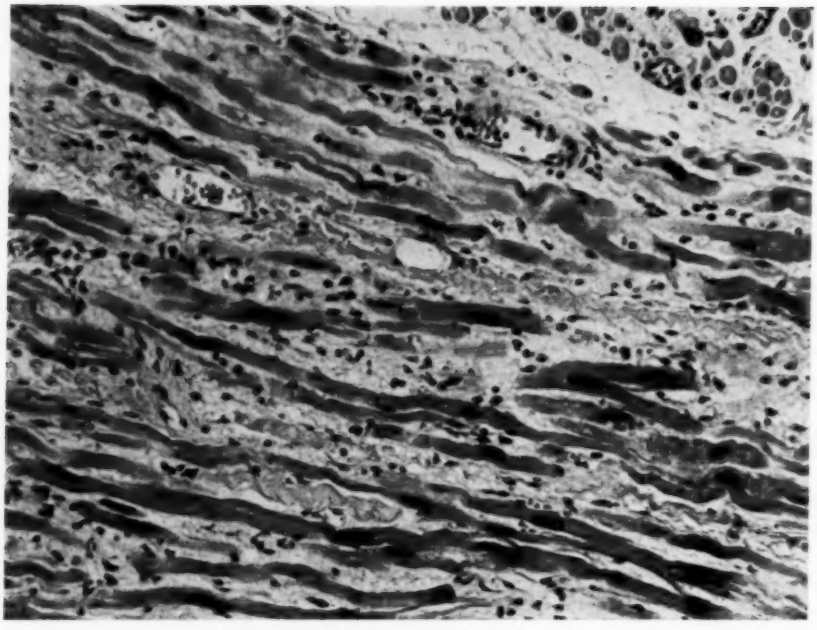

Fig. 7.—Case 6. Note the marked fibrosis extending more or less parallel to compressed and atrophic muscle fibers. There is also a moderate infiltration of small round cells. (Hematoxylin and eosin preparation, ×150).

Autopsy Findings.—There was marked pulmonary edema and pitting edema of the lower extremities and genitalia. There were 1,000 c.c. of fluid in the peritoneal cavity, and 1,000 c.c. of fluid in each pleural cavity. Chronic passive hyperemia of the lungs, liver, and spleen was present. The heart weighed 330 grams. The epicardium was smooth, translucent, and glistening. The right ventricle and atrium were greatly dilated. The left ventricle was moderately firm. The endocardium of all the chambers and the valvular apparatus were intact. The myocardium was moderately firm in part but had a flabby consistency and, on section, appeared mottled. It was tannish-pink to tannish-red, with irregularly shaped, slightly depressed reddish-pink areas scattered throughout. The coronary arteries were free from changes.

Throughout the sections of the myocardium there were areas of fibrosis often running a parallel course to muscle fibers. Commonly, a moderate infiltration of lymphocytes accompanied the course of the connective tissue. Hyalinization of connective tissue fibers was sometimes observed. The perivascular spaces showed a moderate number of histiocytes, myocardial reticulocytes, and an edema-like material. In some of the sections, particularly in those taken from the adjacent endocardium, the connective tissue replacement of muscle fibers was particularly severe. A number of muscle bundles were broken up and disfigured, and individual fibers were flanked by the newly formed connective tissue. There was also an extensive infiltration of lymphocytes, histiocytes, and a number of myocardial reticulocytes. In a few fields the nuclei of remaining muscle fibers were hyperchromatic, assumed bizarre shapes, and seemed extraordinarily large. The endocardium adjacent to such areas showed a new formation of connective tissue, and there were outspoken mural thrombi. Perivascular fibrosis with round cell infiltrations was common. (See Figs. 7 and 8.)

Summary.—A 43-year-old woman developed progressive dyspnea. Following an acute febrile disease, myocardial failure gradually became worse. She had a relentless downhill course, with increasing myocardial failure. Because of a suspected chronic pericardial disease she was operated upon. She died shortly after the operation. Autopsy disclosed an enlarged, flabby heart, which on microscopic examination was the seat of chronic, diffuse interstitial myocarditis. There was no evidence of pericarditis.

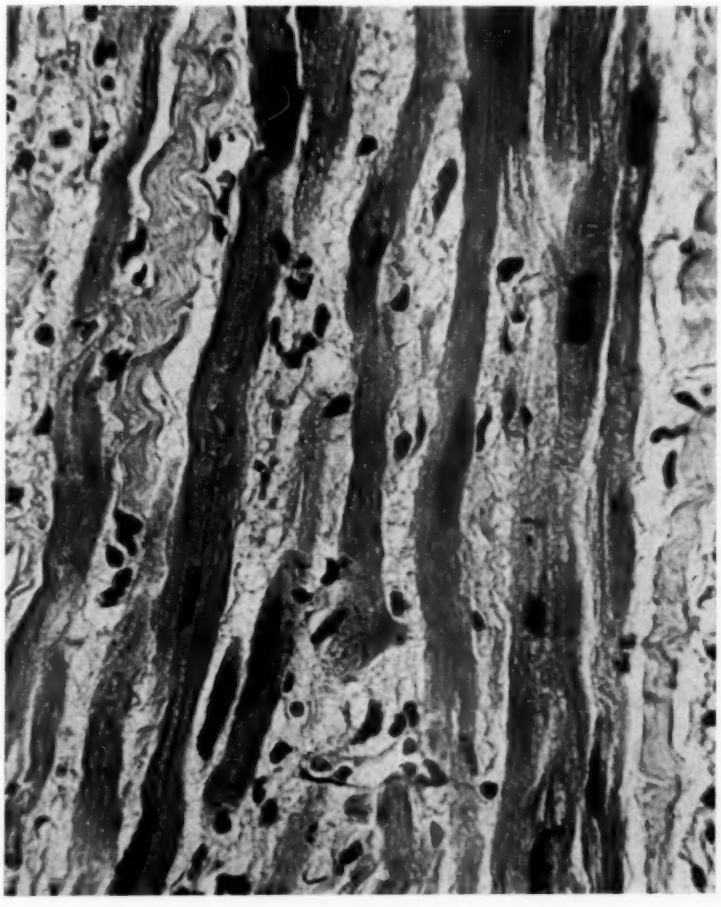

Fig. 8.—Case 6. Note the fibrous connective tissue extending parallel to individual muscle fibers. The latter appear compressed. There is also a moderate number of mononuclear cells. (Hematoxylin and eosin preparation, ×375).

DISCUSSION

From these short case descriptions it is obvious that all 6 of our patients had severe myocardial insufficiency over a prolonged period of time, with a gradually ensuing, more or less relentless downhill course culminating in death. These 6 patients were relatively young. One was an 8½-year-old child, 2 patients were in their twenties, 2 were in their forties, and 1, the oldest, was 50 years old. Three patients succumbed unexpectedly, and 2 died shortly after operative procedures.

A number of the patients had obvious clinical signs of myocarditis. The pulse rate in all of the patients was relatively high, but the temperature was often normal or slightly elevated. A discrepancy between tachycardia and the height of the fever is often found in myocarditis.[21] Tachycardia out of proportion to the height of the fever is usually accepted as very suggestive of myocarditis. This was found in 4 of our patients. Most of the patients had various heart murmurs; in 2 there was a diastolic murmur at the apex which was so pronounced

that these patients were diagnosed as having mitral stenosis. One of these, in whom cardiac catheterization had also disclosed a "mitral block," had been submitted to a commissurotomy operation. Such a diastolic murmur or rumble is usually explained on the basis of "relative" mitral stenosis, because of the dilatation of the left ventricle. A systolic murmur over the precordium was heard in 2 other cases. Such a murmur is likewise heard frequently in cases of both acute and chronic myocarditis. Silber and Saphir[22] again stressed more recently that aortic and mitral diastolic murmurs are more frequent in cases of myocarditis than is generally accepted. Also, pulsus alternans has been reported in myocarditis. It is interesting that our sixth patient was diagnosed clinically as having pericarditis. Balchum and associates[13] and also Kavelman[15] each described a patient who clinically had chronic pericarditis, but in whom the autopsy disclosed chronic myocarditis of the pernicious type.

Gallop rhythm was noted in 2 patients. It is usually remarked that the appearance of protodiastolic gallop rhythm, in the absence of pre-existing heart disease, is reliable evidence of the presence of myocarditis. It is thought to be due to the inflow of blood into a dilated left ventricle during the rapid inflow phase of filling. The persistence of gallop rhythm after full digitalization is a very ominous sign. A small pulse pressure is often seen in patients with myocarditis. This was present in 3 of our patients.

The autopsies also disclosed mural thrombi in 2 of our patients. These thrombi were present in the right auricular appendage. One patient also developed pulmonary emboli. It has been pointed out previously by Saphir and Field,[23] but it is not universally recognized, that mural thrombi are not rarely found in myocarditis.

Outspoken chronic myocarditis at autopsy was found in every one of these patients. In contrast to Fiedler's acute isolated myocarditis, the simultaneous presence of truly chronic inflammation and severe fibrosis is quite characteristic. Most of the patients showed evidence of anasarca and chronic passive hyperemia of the liver, lungs, spleen, and kidneys. All died in congestive failure.

The cause of the myocarditis in our patients is obscure. One patient had a history of pertussis. However, myocarditis following pertussis is extremely unusual.[24] Yet, such a rare complication cannot be ruled out entirely. There was no history or evidence of rheumatic fever in any one of our patients. There was also no history of hypersensitivity. The patient of Case 6 had a history of a febrile disease; however, evidence of myocarditis was present before the onset of the last disease. Although pneumonia was found in some of the patients, it is obvious that myocarditis preceded its onset. There was no disease found at autopsy in the wake of which myocarditis may have occurred as a complication. There was likewise no disease of either the endocardium or pericardium. Thus, the myocarditis must be classified as being of the chronic isolated type.

Clinically, the duration of the disease in 5 of our 6 patients was rather long: at least 6 months in our first patient, 6 years in the second, 2½ years in the fourth, 16 months in the fifth patient, and 10 months in the sixth patient. The duration of the illness in our third patient could not be definitely established because of his mental disturbance, but it was at least of 5 weeks' duration. As stated before,

Fiedler's myocarditis was described as acute myocarditis lasting only a few weeks. Although also "isolated" in the sense that neither the endocardium nor pericardium was involved, myocarditis in our cases was chronic, but with a relentless downhill course, and primarily responsible for the death of the patients.

From the above-quoted references, it also appears that not only isolated myocarditis may cause the clinical picture of chronic pernicious myocarditis, but that any type of myocarditis of known origin may likewise fall into this classification. Two of the above references concern myocarditis following diphtheria and measles, in addition to myocarditis in Chagas' disease.

Lindberg,[6] shortly after Boikan's original description, stated that he did not believe in the justification of classifying pernicious myocarditis as a special or specific entity. His objection was based principally on the observation that there are many myocarditides, both the isolated form and those following various infectious and contagious processes, which may lead to a relentlessly downhill course causing unavoidably the death of the patient. He stressed that there is not one type of myocarditis which in any way is specific and which corresponds to the criteria set forth by Boikan.[4] Although this, of course, is true, it should be underlined that the term "pernicious myocarditis" does not imply a specific lesion in the anatomic sense, but embraces all cases of chronic myocarditis, whatever their origin, which clinically have a gradual downhill course, with remissions and exacerbations, until the patient succumbs more or less unexpectedly. However, as stated, most of the cases in the literature which would fall into the classification of pernicious myocarditis, and all of the cases of pernicious myocarditis which we have observed, are isolated myocarditides of unknown origin, but have a chronic course.

The importance of recognizing pernicious myocarditis lies principally in its grave prognosis. It is realized today that myocarditis is a rather common complication of various infectious and contagious diseases. It seems evident that myocarditis, since it is recognized at autopsies in about 8 per cent of all the cases, probably occurs in an even higher percentage in the living, but apparently some patients recover and remain well. It is only the occasional patient who, after a seeming recovery from myocarditis, may at a subsequent time develop signs and symptoms of early myocardial failure. If this happens once, it is bound to happen again. These are the patients who either become cardiac invalids or recover, only to develop repeated attacks of myocardial decompensation and to succumb to one of these. This realization is implied in the term "pernicious myocarditis."

Not every chronic myocarditis, however, is of the pernicious variety. Rheumatic myocarditis often is chronic, and likewise myocarditides associated with various valvular diseases; but these are not of the pernicious type. Among our 225 cases of myocarditis, there were 39 associated with endocarditis. None of these showed the characteristic clinical features of the pernicious variety. Often, too, so-called chronic myocarditis is not really chronic in the sense of a progressive disease but, incorrectly, refers to myocardial fibrosis, the result of true myocarditis. Although such patients may have had attacks of acute myocarditis in the past, the myocarditis has healed, with scar formation. Such scars are

found occasionally at autopsy, in the absence of any evidence of a progression of the disease. Pernicious myocarditis, on the other hand, shows histologic evidence of a progressive disease, with old fibrous lesions in addition to inflammatory cells characteristic of true chronic inflammation.

From the available evidence it is clear that the most common type of myocarditis which may be classified as "pernicious" is a chronic form of isolated myocarditis, and, to judge from the available literature, also Chagas' myocarditis. As a matter of fact, some of our patients and some of those quoted from the literature present clinical findings quite similar to those found in chronic Chagas' myocarditis. Laranja and associates' description[19] of the clinical course of this myocarditis immediately recalls Boikan's description[4] and also the characteristic clinical findings in our cases.

As stated, the cause of the chronic form of isolated myocarditis appearing as pernicious myocarditis is not known. We and others have studied a number of such cases with all the facilities at our disposal. Nowhere have we encountered any structures in the myocardium which may be interpreted as resembling protozoa, leishmanias, treponemas, etc. Yet, because of the similarity of the clinical picture of chronic Chagas' myocarditis and that of chronic pernicious myocarditis, and, as a matter of fact, also because of the similarity of the nonspecific histologic changes in the myocardium in both of these entities, it might be possible that a living agent is likewise responsible for the chronic isolated myocarditis with the clinical picture of the pernicious form.

SUMMARY

Attention is drawn to a type of chronic myocarditis characterized by a protracted, and yet relentless, downhill course, sometimes with remissions and exacerbations, culminating often in unexpected death. Congestive myocardial failure is very common. Because of the relentless downhill course, the term "pernicious myocarditis" seems appropriate. This type of myocarditis is in no way a specific anatomic entity, and any chronic myocarditis occasionally may cause a protracted and relentless downhill course. However, from our study of the pertinent literature, and from our own observations, it appears that in our geographic region a chronic form of isolated myocarditis is the most common cause.

The etiology of chronic pernicious myocarditis is obscure, just as is that of acute isolated myocarditis (Fiedler's). The resemblance of pernicious myocarditis to chronic Chagas' myocarditis, both clinically and anatomically, is stressed. However, using all of the up-to-date methods of histologic examination at our disposal, we never encountered leishmanias—so common in Chagas' myocarditis—or structures resembling parasites.

Of 225 cases of myocarditis, 6 were reclassified as chronic pernicious myocarditis. The clinical abstracts and autopsy findings of these patients are presented, and the protracted, relentless downhill course with progressive myocardial failure is stressed. Two patients were misdiagnosed as having stenosis of the mitral orifice, and one as having pericarditis. The electrocardiographic

alterations are noted. At autopsy all cases showed a large heart, with no changes in the endocardium or pericardium. On microscopic examination there was a true chronic, mainly interstitial, myocarditis, with young connective tissue compressing and eventually replacing heart muscle fibers, and an interstitial infiltration of inflammatory cells.

The importance of recognizing pernicious myocarditis lies principally in its grave prognosis. After a seeming recovery from a slowly developing illness which may or may not be recognized as myocarditis, the patient shows signs and symptoms of early myocardial failure. Once this happens, it is bound to recur. These are the patients who either become cardiac invalids or recover, only to develop repeated attacks of myocardial decompensation and to succumb to one of these. This realization is implied in the term "pernicious" myocarditis.

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The Jugular Venous Tracing

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Phonocardiography needs reference tracings. A few authors have published phonocardiograms without any reference tracing, but the interpretation may be difficult or impossible even for readers with great experience. The simultaneous recording of two or three phonocardiograms with different filtering yields more information already. The electrocardiogram is frequently used as a reference tracing; it enlarges the information obtained. Yet the electrocardiogram is not the ideal reference for the phonocardiogram. First, the electrocardiographic information is confined to systole. Second, the electrical events do not cover exactly the mechanical events in the heart cycle; in fact, the relationship between the electrocardiogram and the movements of the heart is variable. Third, the electrocardiogram does not enable one to distinguish between left heart and right heart events. For these reasons, the advantage of additional mechanical tracings is evident. To get information about systole and diastole from the left heart and from the right heart, various indirect pulse tracings are necessary. Valuable tracings for this purpose are the carotid tracing, the phlebogram, and the apex cardiogram; the liver pulse and the femoral artery also may be useful. The carotid tracing represents left ventricular ejection; the apex beat furnishes additional information, concerning in particular the left ventricular diastole. The jugular venous tracing and the liver pulse reflect systolic and diastolic events in the right heart. Therefore, by successively recording the pulsations of the carotid artery, the jugular vein, and the apex beat it is possible to study the systolic and diastolic part of the heart cycle in both the left and the right heart. Sometimes, however, the apex beat is formed by the right rather than by the left heart, and in this case we fail to have information about left-sided diastolic events. To distinguish between the apex beat from the left heart and that from the right heart, several methods are available. The two most important are the precordial electrocardiogram taken exactly at the site of the apex beat, and the correlation of the jugular venous and apex beat tracings, as shown in the exhibit of the Leiden Cardiac Center at the Third World Congress of Cardiology in Brussels (see also Snellen[19,20]; detailed publication is being prepared). In order

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to obtain synchronously an electrocardiogram, two phonocardiograms of different frequency, and a pulse tracing, the use of a four-channel apparatus is necessary. Therefore, we feel that for efficient phonocardiographic examination, equipment capable of reproducing four tracings simultaneously is essential.

The various pulse records are of value as a reference for the phonocardiogram and because of the shape of the pulse tracing. Examples of the latter use are the characteristic patterns of the carotid artery in aortic stenosis and aortic insufficiency; the positive venous and liver pulse tracing in tricuspid insufficiency; the different forms of the apex cardiogram in mitral stenosis and mitral insufficiency, as well as in atrial septal defect and ventricular septal defect; and the slow ascent of the external femoral arterial tracing in coarctation of the aorta. The value of these pulse records as reference tracings for the phonocardiogram is obvious if one thinks of the relationship of the ejection sound and of the two components of the second sound with the carotid artery; of the tricuspid opening snap and of the third sound from the right heart with the venous tracing; and finally, of the mitral opening snap and the third sound from the left heart with the apex cardiogram. In fact, without pulse tracings it is impossible to make a reliable diagnosis of the 15 various sounds presently known.*

In 1957, Cossio and Buzzi[4] published an interesting article about the clinical value of the venous pulse. They paid full attention to the form of the venous pulse, but little to its value as a reference tracing for the phonocardiogram.

During the European Congress of Cardiology in Stockholm (1956) and the World Congress of Cardiology in Brussels (1958), we demonstrated in an exhibition room these combined tracings.[8,9,19,20] In this paper we will report our experience with the venous tracing, although we want to stress that a study of all the various pulse tracings is necessary for a complete understanding of the hemodynamics of the patient. This communication is based on a study of about 10,000 phonocardiograms. Many patients underwent right heart catheterization. Furthermore, surgery has allowed us to compare in a number of these patients the phonocardiographic interpretations with the operative findings and to study these patients before and after operation. The records are made photoelectrically with a piezoelectric microphone. The apparatus used is the five-channel Hellige Multikardiotest Type 9900/5. The paper speed is 50 mm. per second, and the time between the small lines is 0.02 second. The synchronous electrocardiogram is Lead II; the uppermost phonocardiogram is an intermediate-frequency tracing and the lowermost one is a high-frequency tracing, designated according to Maass and Weber as 70 Herz and 140 Herz, respectively.[15]

The various pulse tracings are made with the same applicator, consisting of a small cup connected by an air-containing rubber tubing to a linear crystal microphone. The cup is held by hand. The best place for taking a venous tracing is close to the median line of the chest just above the right clavicle, in such a way

*Mitral and tricuspid closure sound, aortic and pulmonic ejection sound, midsystolic extra sound, aortic and pulmonic closure sound, mitral and tricuspid opening snap, third sounds from left and right heart, atrial sounds from left and right heart, summation gallop sound, sound of transient closure of the A-V valves before ventricular contraction. (So far, no distinction between left and right heart was possible in the two latter cases.)

that the membrane of the cup faces the diaphragm and the rim of the cup pushes the carotid artery aside, thus avoiding interference of the carotid pulse with the venous pulse. Even in patients with strong arterial pulsations, we have obtained undistorted venous tracings in this way. The patient is placed in a supine position, with complete muscular relaxation, and the tracing is taken in normal expiratory apnea.

The venous tracing appears to be more variable than other pulse tracings. This is due partly to the fact that the venous tracing is, for the most part, recorded in diastole; it is well known that diastole varies more than does systole.

Fig. 1.

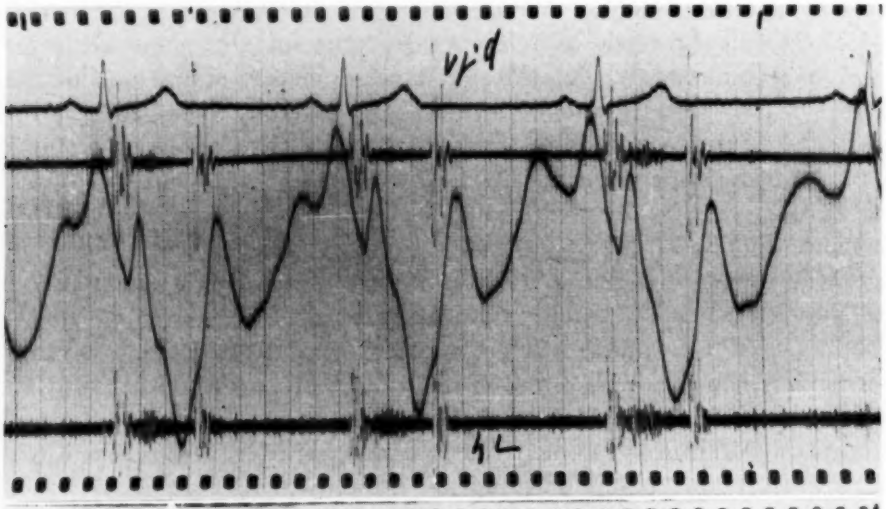

Fig. 2.

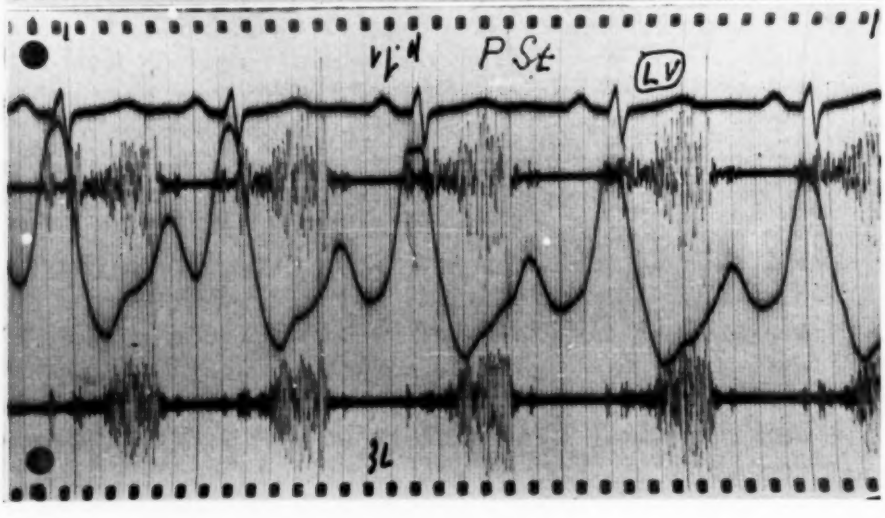

Fig. 1.—Complete venous tracing. The *a* wave is the highest of the four positive waves. It begins 0.06 sec. after the beginning of the P wave and reaches its summit 0.14 sec. after the beginning of the P wave. The *x* depression ends before the split second sound and is deeper than the *y* depression. The *h* wave occurs 0.80 sec. after the beginning of the main deflection of the electrocardiogram.

Fig. 2.—Venous tracing in pulmonic stenosis. The atrial sound, visible in the 70 Hz (second tracing from above) and the 140 Hz phonocardiogram (fourth tracing from above), coincides with the summit of the *a* wave. The pulmonary component of the second sound (visible in both phonocardiograms) is quite close to the summit of the *v* wave.

A complete venous tracing is obtained only with a slow heart rate, diastole then being long. It is represented by four positive waves and two depressions (Fig. 1).

The positive waves are: (1) the *a* wave produced by atrial contraction; (2) the *c* wave due to right ventricular contraction; (3) the *v* wave due to the completion of venous filling of the right atrium while the tricuspid valves are closed; and (4) the *h* wave, marking the end of complete filling of the right ventricle.

There is general agreement that the systolic or *x* depression is caused by atrial diastole and lowering of the bottom of the right atrium by right ventricular contraction. The diastolic or *y* depression is due to the emptying of the right atrium after opening of the tricuspid valves. Normally, the *x* depression is deeper than the *y* depression. Paul Wood[21] gives the following typical figures for the height of the various waves: $a = 0$; $x = -4$; $v = 0$; $y = -3$; $h = -1$ (called *z* by Wood). Fowler, Westcott and Scott,[6] from a large group of observations on normal subjects, quote the following average atrial pressures for the various waves: $a = 5.5$; $c = 3.5$; $v = 4.5$; $x = 1.5$; $y = 2.5$. The pressures are given in millimeters of mercury from a line 10 cm. anterior to the spine. These figures are in good agreement with the relative height of the waves as found by us in the jugular venous tracings. They do not agree with the venous tracings published by Altmann.[1,2] Altmann registers the visible pulsations of the external jugular vein by means of a beam of light crossing the vein and directed to a photocell. We feel that these visible pulsations often are of combined venous and arterial (carotid) origin, causing the *c* wave to be higher than the *a* and *v* waves, and the *x* depression to end 0.02 second after the second sound, as does the carotid catacrotic incisura. Zeh,[22] employing the same method as Altmann and Weber, states that the transmission from the right atrium to the jugular vein amounts to only a few hundredths of a second for the different waves, except for the end of the *x* depression, which should have a delay of 0.24 second. In our opinion, this seemingly excessive delay of the *x* depression in the venous tracing is due to disturbance of the phlebogram by the carotid pulsations. In agreement with many other workers in this field, we have found the end of the *x* depression in the phlebogram to occur before the second sound. The transmission from the right atrium to the jugular veins will be discussed further in the course of this article.

The *a* wave in the venous tracing begins about 0.05 second after the beginning of the P wave in the electrocardiogram and reaches its summit after another 0.11 second. The jugular venous *a* wave is thought to be due to regurgitation of blood from the atrium into the veins. If the resistance to ventricular filling is increased, the *a* waves are higher, because more blood is regurgitated. The tall *a* wave may be associated with an atrial sound in the phonocardiogram if the increased resistance is caused by a higher ventricular end-diastolic pressure. This will be the case in pulmonic stenosis and in pulmonary hypertension from any cause. If the increased resistance to ventricular filling is due to a narrowed tricuspid valve, an atrial systolic murmur may appear. It must be noted, however, that there is no general agreement concerning the graphic definition of a heart sound as differentiated from a murmur, and it may be doubtful in some cases whether the recorded vibrations represent a murmur or a sound. The venous

tracing may be of help then because an atrial sound from the right heart is synchronous with the summit of the *a* wave, as we have found in our venous tracings (Fig. 2), whereas the atrial systolic murmur starts before this summit. Kuo[12] found that in auricular gallop the gallop sound occurred at the peak of the atrial *a* wave in the pressure curve. This has also been our experience. Since we also have found the atrial sound to be synchronous with the peak of the jugular *a* wave, little or no delay in transmission from the right atrium to the jugular vein is to be accepted. This is in contrast to the opinion of Kuo, who observed a delay of 0.16 to 0.20 second in the transmission of the venous pulse wave from the right atrium to the jugular vein. Lagerlöf and Werkö,[13] in an earlier study, stated that the summit of the *a* wave in the phlebogram appears 0.08 second after the corresponding wave in the right atrial pressure curve, and they found a delay of the *v* wave in the jugular vein as long as 0.13 second. The published tracings in the last article, however, show distorted atrial pressure curves and venous pulse curves influenced by carotid pulsations. The point *x* falls then after the second sound, and the recorded (false) *v* wave occurs too late. If, indeed, the transmission from the right atrium to the jugular vein were as poor as Kuo and Lagerlöf and Werkö state, the venous tracing would be worthless as a reference tracing for the phonocardiogram.

Margolies and Wolferth,[16] however, stated already in 1932, that the opening snap in mitral stenosis was synchronous with the top *v* of the venous tracing. Although the mitral opening snap is a left-sided phenomenon, a delay of 0.13 second for the jugular *v* wave would be incompatible with the statement of Margolies and Wolferth. Eddleman and associates[5] found in several subjects in whom atrial pressure curves were obtained during cardiac catheterization, no appreciable difference in time between the fall of the atrial pressure and the peak of the *v* wave in the jugular venous pulse. This agrees with our findings. During cardiac catheterization we obtained synchronously a pressure tracing from the right atrium and an external jugular venous tracing, and found constantly no appreciable difference in time between the summits of the *a* and the *v* waves in the right atrial pressure tracing and in the jugular venous tracing.[10] Furthermore, we recorded apex cardiograms in all of our patients. The apex cardiogram shows no appreciable time lag. In several patients we got an apex beat from the right heart. The correlation between the apex beat from the right heart and the venous pulse tracing was manifest in all of our patients, showing that the delay in transmission to the jugular vein in external tracings can be neglected. Even in those cases in which only a left apex beat tracing was recorded, the asynchronism between the venous tracing and the apex beat never reached such figures as Kuo and Lagerlöf and Werkö stated for the delay from the right atrium to the jugular vein. It must be concluded from our observations that the lag in time between the atrial pressure tracing and the external jugular venous tracing is negligible, and that the phlebogram is a suitable reference tracing for the phonocardiogram.

In the presence of a long P-R interval a high-pitched sound may be seen in the phonocardiogram 0.22 to 0.30 second after the onset of the P wave (Fig. 3). In the phlebogram this sound corresponds to the end of the descending limb of

the *a* wave and probably represents transient closure of the atrioventricular valves, caused by a positive ventricular-atrial pressure gradient at this moment.[11,12,15,16]

The amplitude of the *a* wave is also related to the heart rhythm. When atrial contraction occurs early in diastole before the rapid filling of the right ventricle is completed, the resistance to ventricular filling is small, and little or no regurgitation takes place in the veins. This may be found in tachycardia, or in complete

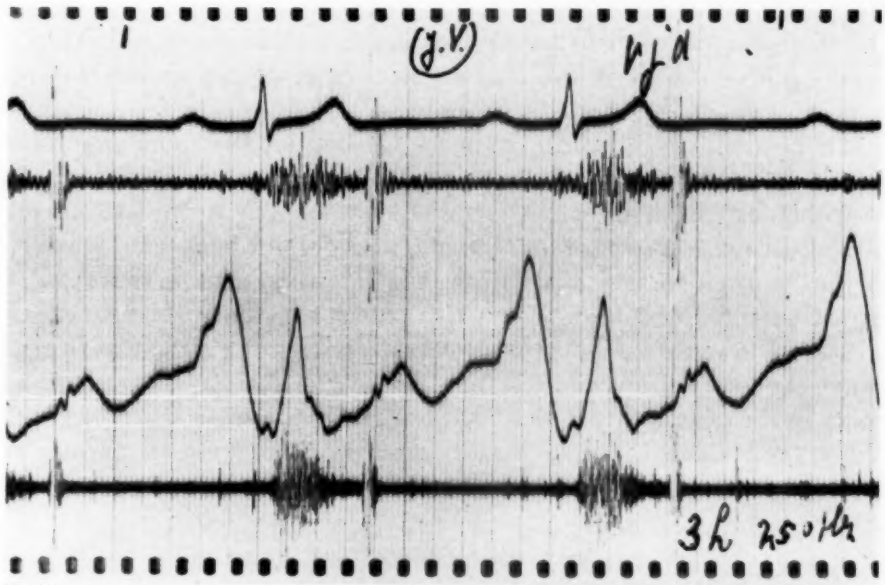

Fig. 3.

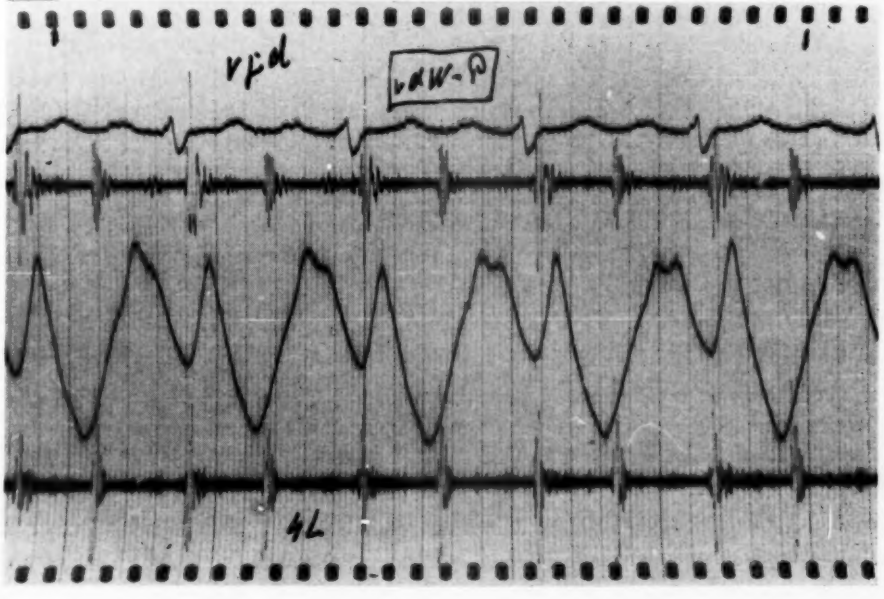

Fig. 4.

Fig. 3.—An atrial sound coincides with the summit of the jugular *a* wave. A high-pitched sound occurs at the end of the *a* descent, probably representing transient closure of the A-V valves. The presence of this sound is dependent on the existence of prolonged A-V conduction.

Fig. 4.—Venous tracing with merging *v* and *a* waves due to early appearance of the *a* wave.

and incomplete atrioventricular block. In the phlebogram this is reflected by the fall of the *a* wave in the descending limb of the *v* wave, which results in a small *a* wave (Figs. 4 and 5). Even in pulmonic stenosis the *a* wave may be small when it appears early in diastole.

When atrial and ventricular systole coincide, ejection of blood from the atrium is only possible toward the veins, resulting in giant *a* waves (Venenpropfung; ventricular tamponade) (Fig. 5).

The *c* wave is due to right ventricular contraction and occurs simultaneously with the first heart sound and before the rise of the carotid tracing (Fig. 6). In many tracings there is also a later appearing *c* wave, due to arterial interference; in fact, in some tracings this will be the only *c* wave. The occurrence of the arterial *c* wave is dependent upon the kind of heart disease, but still more upon the training of the investigator. That the real venous *c* wave is not an arterial impact may be concluded from its being recorded in the right atrial pressure tracing and in the liver pulse tracing. Furthermore, in atrial fibrillation the *c* wave in the phlebogram is often smaller after a long diastole than after a short one; this is in contrast to the arterial tracing, which shows constantly higher waves after a long diastole than after a short one. The location of the *c* wave with regard to the *a* wave is dependent on the P-R interval in the electrocardiogram. It appears commonly in the descending limb of the *a* wave, in the first part of the *x* depression. When the P wave in the electrocardiogram occurs during ventricular systole, the *c* wave appears before the *a* wave, or the *c* and *a* waves merge into one wave (Fig. 5).

During ventricular systole, venous blood continues to flow into the atrium. Toward the end of ventricular systole the atrium is filled up and the venous curve starts to rise, thus forming the ascending limb of the *v* wave. The descending limb of the *v* wave begins with the opening of the tricuspid valves, and the onset of this descending limb is termed the summit of the *v* wave. It is possible that a slight descent of the *v* occurs before or at the second sound, but the opening of the tricuspid valves is marked then by an increasing speed of descent. In pulmonic stenosis the pulmonary component of the second sound is quite close to the summit of the *v* wave (Fig. 2). The same holds true in cases of atrial septal defect with normal pulmonary pressure (Fig. 6). In pulmonic stenosis the time between the pulmonary part of the second sound and the summit of the *v* wave is less than 0.04 second and may be zero. This finding was so constant in our series of cases of pulmonic stenosis that it seems reasonable to assess the degree of splitting of the second sound from the time elapsing between the aortic part of the second sound and the summit of the jugular *v* wave in those patients with pulmonic stenosis in whom the pulmonary part of the second sound could not be recorded in the phonocardiogram. In atrial septal defect the time between the pulmonary component of the second sound and the summit of the *v* wave may amount to 0.06 second, if the pulmonary pressure is not appreciably elevated. The somewhat higher pulmonary pressure in atrial septal defect, as compared with the abnormally low pressure in pulmonic stenosis, is thought to be the reason that the distance between the pulmonary part of the second sound and

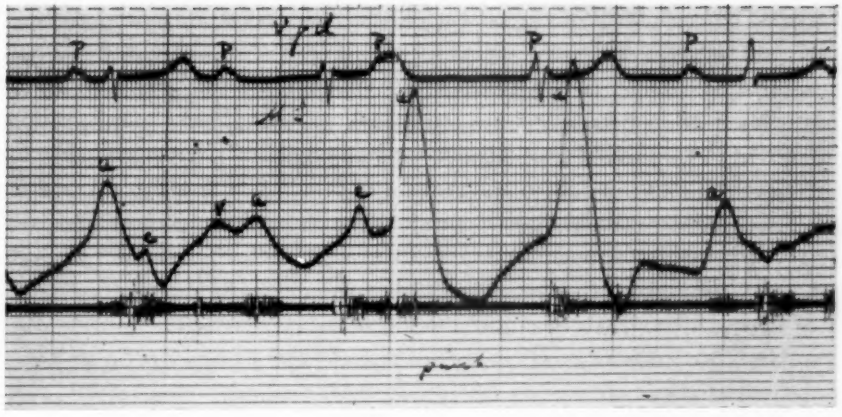

Fig. 5.—The first cycle shows a normal *a* wave. In the second cycle the *a* appears in the *v* descent and is low. In the following cycles, atrial contraction occurs during ventricular systole, resulting in tall *a* waves.

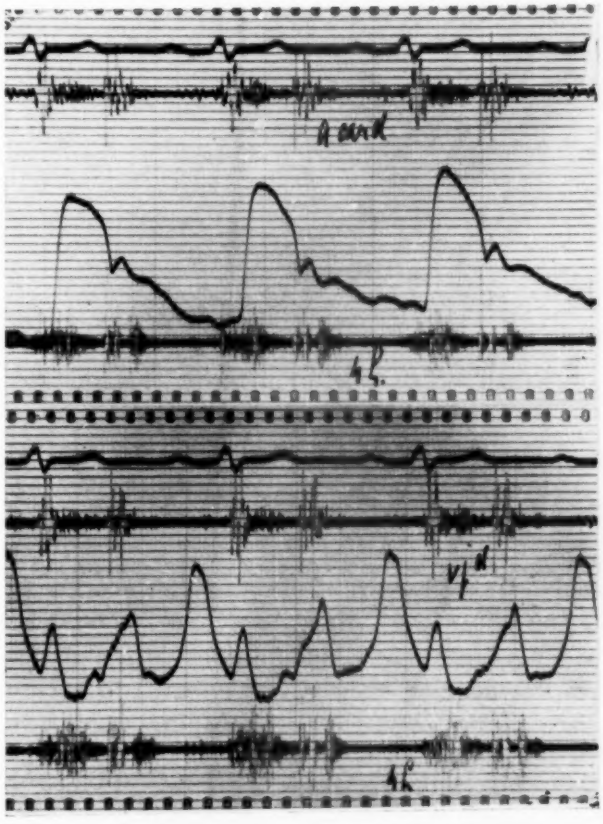

Fig. 6.—Atrial septal defect. Above is the pulse tracing from the carotid artery; below is the jugular venous tracing recorded on the same patient. The carotid artery tracing starts significantly later than the venous *c* wave. The pulmonary component of the second sound occurs 0.05 sec. before the summit of the *v* wave; the mid-diastolic murmur starts after this summit, is maximal during the *v* descent, and stops with the end of rapid filling of the right ventricle (see lowermost phonocardiogram).

the summit of the *v* wave is slightly greater in atrial septal defect than in pulmonic stenosis. However, if the atrial septal defect is complicated by pulmonary hypertension, the time between the pulmonary part of the second sound and the summit of the *v* wave increases and, in our experience, may be as much as 0.12 second (Fig. 7). This holds true also for other cases of pulmonary hypertension. The explanation would seem to be that in cases of low pulmonary pressure the closure of the pulmonary valves precedes the tricuspid opening by only some hundredths of a second or less, whereas in pulmonary hypertension the pulmonary valves close earlier, and the time between closure of the pulmonary valve and opening of the tricuspid valve is increased. In the latter case the hemodynamics are more like those in the left heart, in which the closure of the aortic valves precedes the opening of the mitral valves by about 0.10 second.

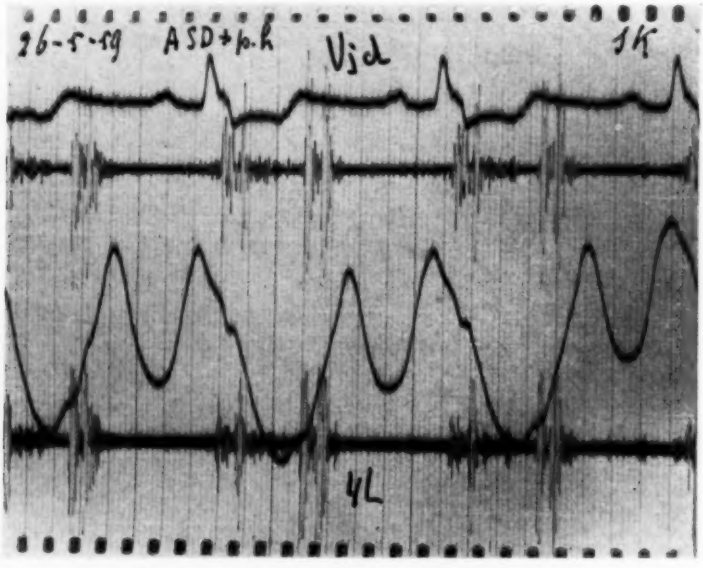

Fig. 7.—Atrial septal defect with pulmonary systolic pressure of 80 mm. Hg. An ejection sound is recorded after a split first sound. The summit of the *v* wave appears 0.11 sec. after the pulmonary component of the second sound.

As published by Margolies and Wolferth,[16] the mitral opening snap is simultaneous with the summit of the venous *v* wave, if the right and left heart events coincide. This is in agreement with our findings, although we have to state that in mitral stenosis the opening snap may be found to occur shortly before the summit of the *v* wave, even in cases in which splitting of the second sound is not obvious. The tricuspid opening snap which occurs in tricuspid stenosis, but which is more frequently encountered in atrial septal defect, was always found on the top of the venous *v* wave (Fig. 8). This opening snap was often not audible because of its very short distance from the second sound and was recorded in 15 out of 91 cases of atrial septal defect in which operation revealed normal tricuspid and mitral valves. We have to allow for the possibility that the tricuspid opening snap is still more frequent in atrial septal defect, because in 5 additional

cases the last vibration of a broad, high-pitched pulmonary component of the second sound coincided with the summit of the *v* wave and possibly represented an opening snap.

The descending limb of the *v* wave is inscribed during the rapid inflow into the right ventricle. The end of the steep descent corresponds to an eventual third sound from the right heart (Fig. 11). A third sound from the left heart is often earlier and occurs commonly in the descending limb of the *v* wave. Consequently, a third sound occurring before the *y* depression is from the left heart; a third sound at the end of the *v* descent may be either from the left heart or from the right heart. If both third sounds are recorded, the determination is easy (Fig. 9). Calo[3] described a fifth sound, occurring later than the third sound. In our tracings an additional diastolic sound, occurring after a third sound, was always synchronous with the *y* depression of the venous tracing and was thought to be a

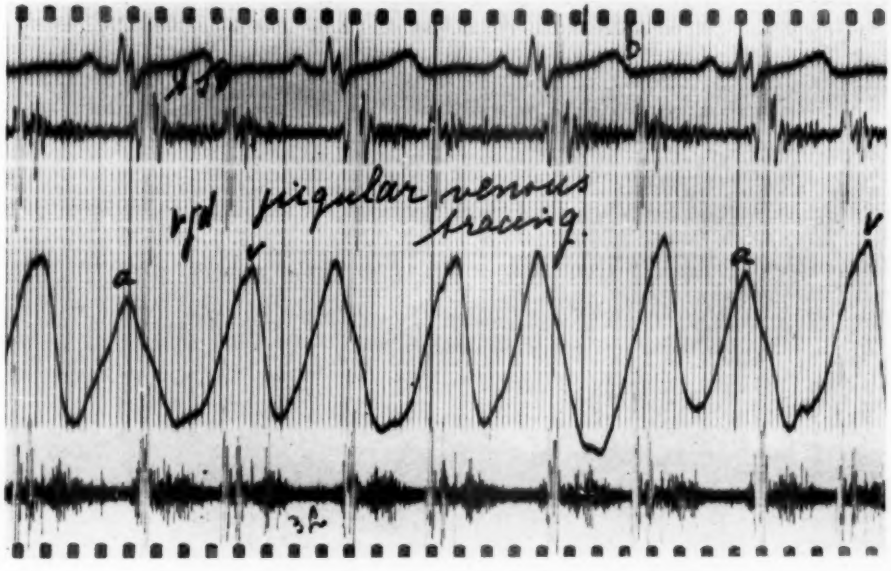

Fig. 8.—Atrial septal defect. A tricuspid opening snap appears after a widely split second sound and is synchronous with the summit of the *v* wave. A short mid-diastolic murmur occurs during the rapid filling of the right ventricle. The *v* wave is slightly higher than the *a* wave. The summit of the *v* wave appears 0.04 sec. after the pulmonary part of the second sound, indicating normal pulmonary pressure, as was indeed found by right heart catheterization. At operation the atrial septal defect measured 4 by 4 cm.; no tricuspid regurgitation was felt; tricuspid and mitral valves were normal.

third sound from the right ventricle. Therefore, we suppose that the fifth sound mentioned by Calo is identical with the third sound from the right heart. Because of the fact that a third sound from the left heart is much more frequent than one from the right heart, the general statement found in the literature is that the third sound supervenes in the descent of the *v* wave.[16] The physiologic third sound is probably always from the left heart. The difference in incidence between the third sound from the left heart and that from the right heart is in agreement with the diastolic contour of the apex beat tracings, just as the rapid filling wave is more conspicuous in the left apex cardiogram than it is in the right apex

cardiogram. This is also in accordance with the venous tracing, because after the steep descent, representing the rapid atrial outflow, the tracing often does not rise immediately, but before rising continues descending, with a smaller slope, indicating that the atrial outflow into the right ventricle is still greater than the venous inflow into the right atrium. The transition from rapid to slow filling is apparently less abrupt in the right ventricle than in the left ventricle, and this may allow for the greater incidence of a third sound from the left heart than from the right heart.

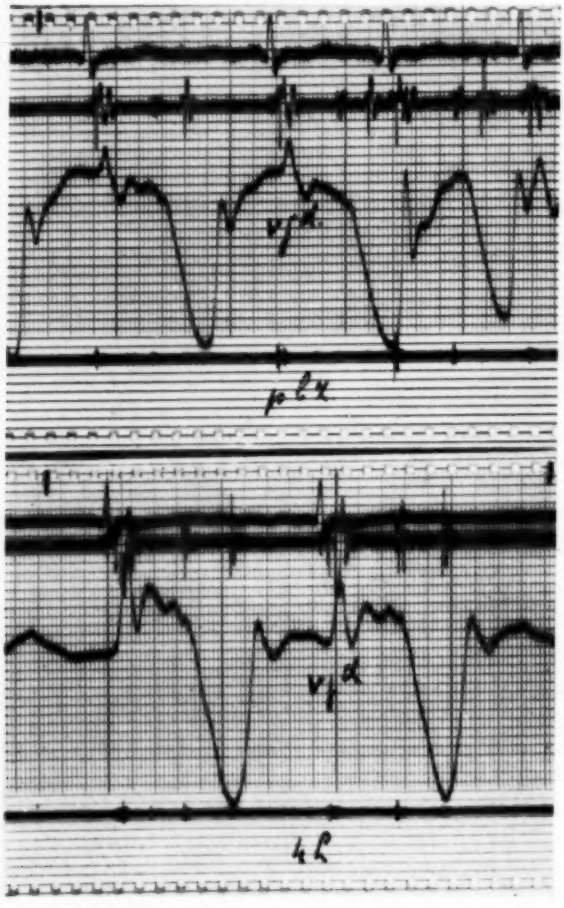

Fig. 9.—Venous tracing in constrictive pericarditis. The top picture shows in the intermediate frequency a third sound, recorded at the apex, and occurring in the descent of the *v* wave. It is thought to be a third sound from the left heart. The lower picture (from the same patient) shows a later appearing third sound, recorded in the fourth intercostal space parasternally and coinciding with the *y* depression, therefore presumably originating from the right heart.

In atrial septal defect a mid-diastolic murmur attributed to relative tricuspid stenosis, and a protodiastolic murmur referred to pulmonary incompetence, have been described by many authors. We have found a diastolic murmur in 80 per cent of 91 cases of atrial septal defect in which at operation the mitral and tricuspid valves were found to be normal. In many cases, however, it was

not possible to determine with certainty whether the murmur was protodiastolic or mid-diastolic, because of the fact that the pulmonary component of the second sound appeared very shortly before the opening of the tricuspid valves, occurring close to the summit of the *v* wave (Figs. 6 and 8). In the left heart the difference between a protodiastolic and a mid-diastolic murmur is more apparent. The end of the diastolic murmur in every patient with uncomplicated atrial septal defect was reached at or very shortly after the *y* depression in the phlebogram.

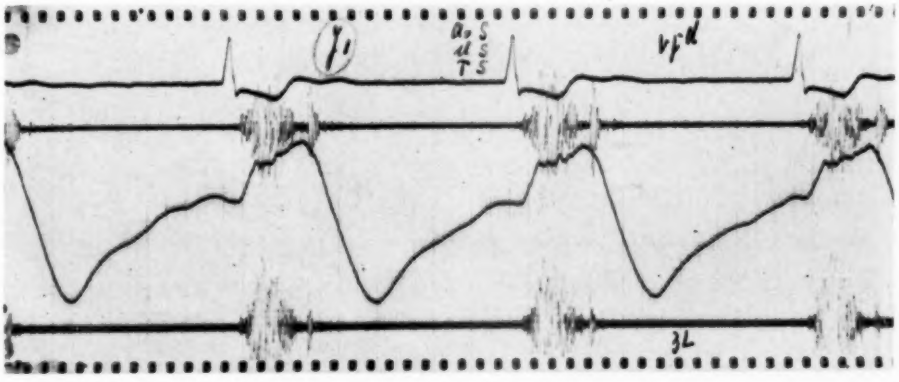

Fig. 10.—Venous tracing in predominant tricuspid stenosis, confirmed at operation. The *h* wave is late or absent, and both limbs of the *y* depression have a smaller slope than usual.

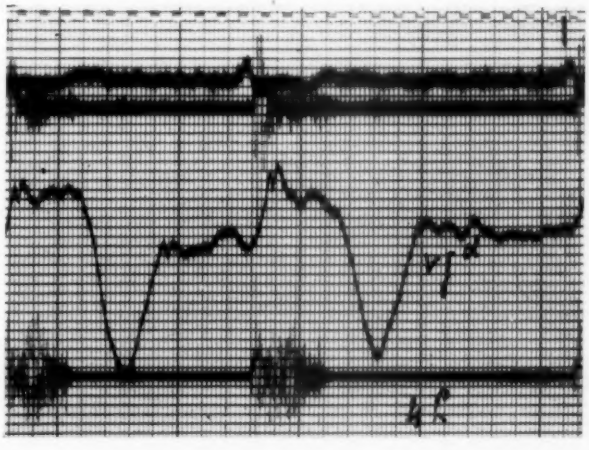

Fig. 11.—Venous tracing in predominant tricuspid insufficiency. This patient was operated on for pulmonic stenosis. Apart from the pulmonic stenosis the surgeon found tricuspid regurgitation. The *x* depression is absent, a well-formed *y* depression is present, and in the intermediate phonocardiogram a third sound, probably from the right heart and synchronous with the *y* depression, is recorded. The *h* wave appears 0.76 sec. after the Q wave of the electrocardiogram.

As for the mid-diastolic murmur, due to augmented flow through normal tricuspid valves, it is acceptable that after the rapid filling the remaining flow is not sufficient to produce a murmur. In the same way, however, the protodiastolic murmur of pulmonary insufficiency stops at the *y* depression if the pulmonary pressure is not raised, as we have noted in those patients who demonstrated pulmonary

insufficiency after operation for pulmonic stenosis. Even a loud protodiastolic murmur did not reach beyond the *y* depression, and the murmur was recorded in the phonocardiogram in the shape of a short diamond, immediately following the pulmonary part of the second sound, if present, or following the aortic part

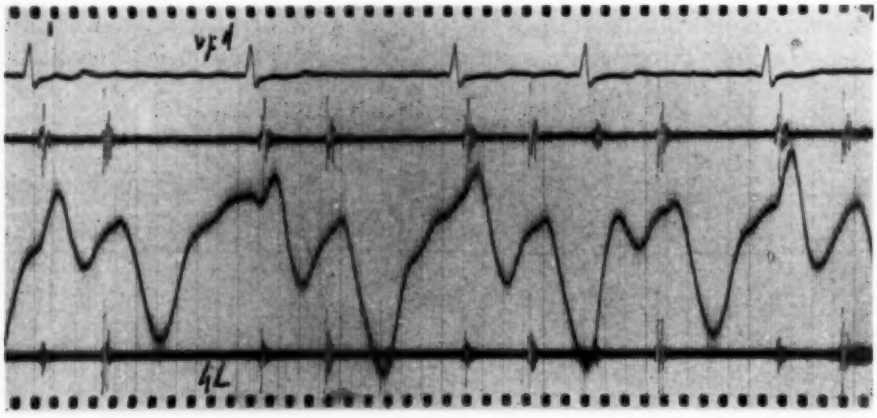

Fig. 12.—Venous tracing in atrial fibrillation. The *a* wave is absent and the *y* depression is deeper than the *x* depression; when diastole is sufficiently long, an *h* wave is present.

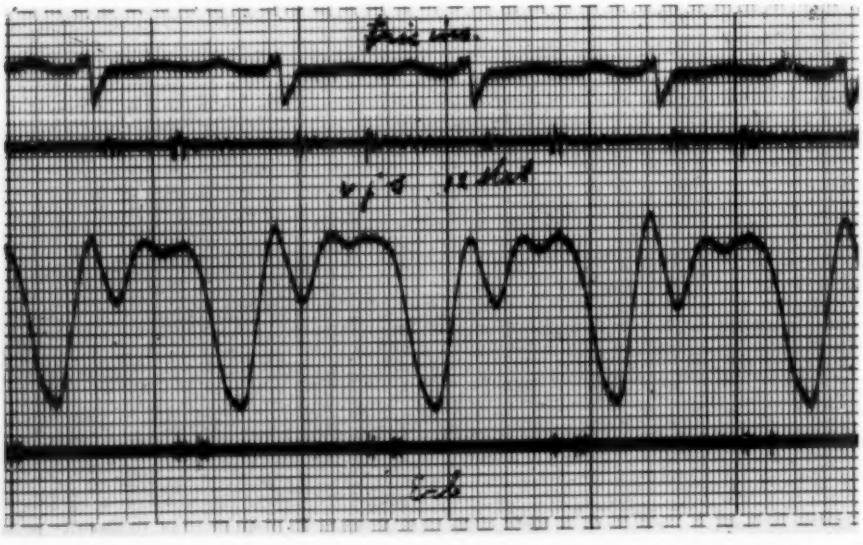

Fig. 13.—Venous tracing in a patient with tricuspid insufficiency with sinus rhythm. The *x* depression is present after the *a* wave, but is filled up after the *c* wave. After the patient was effectively treated, the venous tracing was normal 5 days later.

of the second sound after a silent gap. The murmur may be thought to represent a mid-diastolic murmur when the pulmonary component of the second sound is absent. Only in the presence of pulmonary hypertension may the pulmonary protodiastolic murmur extend beyond the *y* depression, as does the aortic protodiastolic murmur in aortic insufficiency. Also, the diastolic murmurs of tricuspid

and mitral insufficiency stop at or shortly after the *y* depression, because they are due to augmented flow in early diastole, whereas the diastolic murmurs of tricuspid and mitral stenosis may pass distinctly beyond the *y* depression.

After the rapid ventricular filling the venous tracing either shows a slower descent before rising again or rises immediately. If the heart rate is slow, the

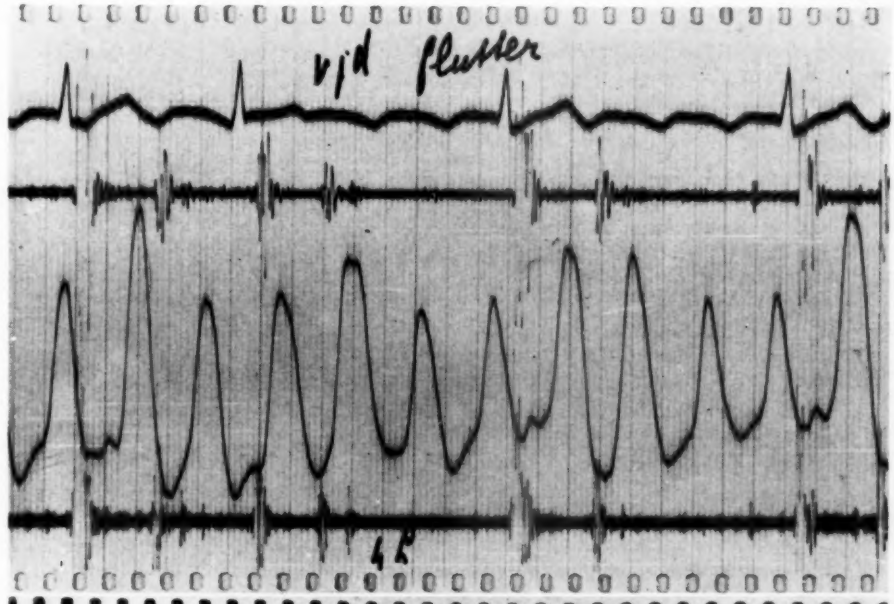

Fig. 14.

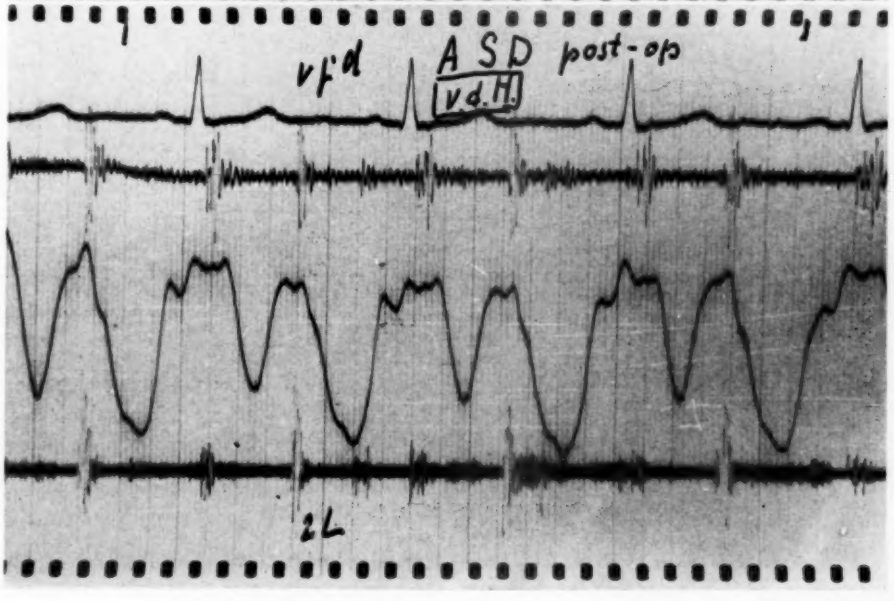

Fig. 15.

Fig. 14.—Venous tracing in atrial flutter. The multiple *a* waves are predominant. If the *a* wave occurs during ventricular systole, the *a* wave becomes higher.

Fig. 15.—Venous tracing in atrial septal defect after operation. The *a* wave is small or absent, the *x* depression is only present after the *c* wave, and the *y* depression is deeper than the *x* depression. The second sound is narrowly split and close to the summit of the *v* wave.

y depression is followed by the *h* wave, marking the end of slow filling of the right ventricle. This wave was first described by Hirschfelder,[11] in July, 1907. He encountered in some venous tracings a wave which occurred after the collapse following the *v* wave, and noted that the wave corresponded more or less to the time at which the cardiac plethysmograph showed that the main filling of the

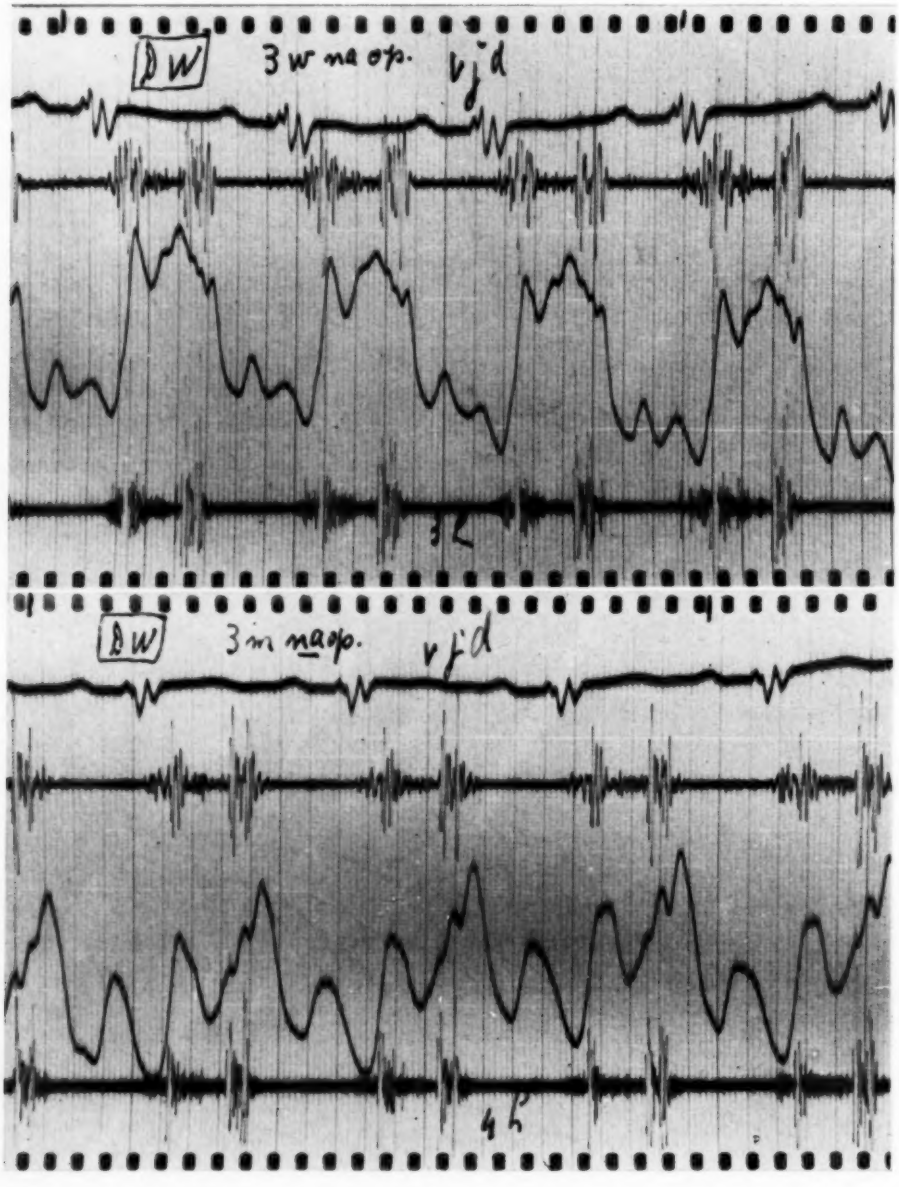

Fig. 16.—*A*, Atrial septal defect of the primum type after operation without closure of the defect. The venous tracing was taken 3 weeks after operation and shows an indistinct *a* wave, a shallow *x* depression after the *c* wave, and a deep *y* depression. The pulmonary component of the second sound is close to the summit of the *v* wave. In the phonocardiogram an ejection sound is recorded. *B*, The same patient 3 months after operation. The *a* wave is more pronounced than in *A*. *C*, The same patient 6 months after operation. A distinct *a* wave is present. The *y* depression is still somewhat deeper than the *x* depression.

ventricle had occurred. In the same year, November, 1907, Gibson wrote: "In the course of a study of jugular pulses in normal persons I have noticed that in those whose pulse rate is slower than the average a wave between the "v" wave and the "a" wave is often to be seen. It is conceivable that this extra wave may be due to the closure of the atrioventricular valves by natural filling of the ventricle with blood."[7] Both authors suggested that this extra wave might coincide with the third heart sound, and Gibson even wrote to Einthoven, who had recorded the third heart sound, to ask for information about the location of this sound.

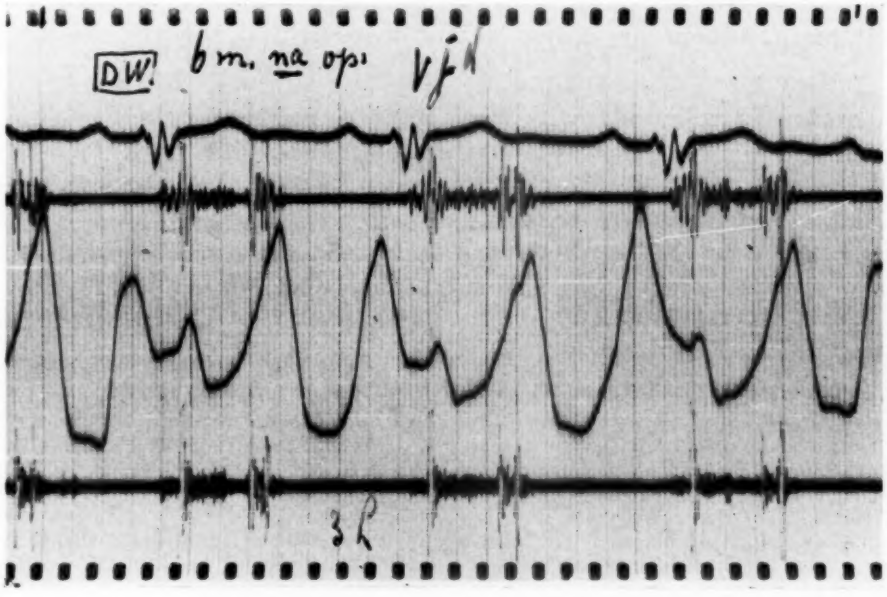

Fig. 16.—*C.* *(For legend see opposite page.)*

The *h* wave may be present either as a distinct positive wave (Figs. 1 and 9) or only as the onset of a horizontal line, the latter representing the base line of the phlebogram (Fig. 11). With increasing heart rate the *h* wave disappears, and the *y* depression is followed by the *a* wave of the next heart cycle (Fig. 7). With still increasing heart rate, even the *y* depression may be absent, and *v* and *a* merge into one single wave (Fig. 4). The usual location of the *h* wave is some 0.40 second after the second sound and 0.80 second after the Q wave of the electrocardiogram. In severe constrictive pericarditis the *h* wave occurs early. The ventricle is not able to dilate further after the rapid filling, and the rise after the *y* depression is abrupt, giving origin to a deep, narrow *y*-trough and an early *h* wave (Fig. 9). In great contrast to the picture in constrictive pericarditis is the venous tracing in tricuspid stenosis. Here the *y* depression is shallow and the *h* wave is late or absent (Fig. 10), as already described by Wood.[21] The rapid and the slow filling through a narrowed tricuspid orifice are retarded, and the descending as well as the ascending limbs of the *y* depression show a decrease of their slope.

In predominant tricuspid insufficiency there is a deep *y* depression and a distinct *h* wave which may be earlier than usual (Fig. 11). These factors may be of interest even if the patient had a right heart catheterization. We have found a diastolic pressure gradient between the right atrium and the right ventricle of 5 mm. Hg which was thought to be proof of tricuspid stenosis, whereas operation revealed tricuspid insufficiency without stenosis. The venous tracing, however, presented distinct *h* waves. In recent years we have been able to avoid this mistake by appreciating the venous tracing while bringing down the heart rate if necessary in order to obtain sufficient diastolic time for recording the *h* wave.

With atrial fibrillation, the part of the *x* depression due to atrial diastole is absent, and results in a *y* depression that is deeper than the *x* depression (Fig. 12).

In tricuspid insufficiency with sinus rhythm the regurgitant flow from the right ventricle to the right atrium may fill up more or less the *x* depression in the phlebogram, and the *y* depression may be deeper than the *x* depression, as in atrial fibrillation without tricuspid insufficiency. However, in tricuspid insufficiency the *x* depression after the *a* wave remains, and it is only from the *c* wave on that the *x* depression is flattened out or filled up (Fig. 13). This is in contrast to the venous tracing in atrial fibrillation without tricuspid insufficiency, wherein the *x* depression after the *c* wave is present (Fig. 12). If tricuspid insufficiency supervenes in a patient with atrial fibrillation, the *x* depression after the *c* wave is absent, and *c* and *v* make one positive wave (Fig. 11).

With atrial flutter the venous tracing is quite different from that in atrial fibrillation. In atrial flutter the multiple *a* waves are predominant (Fig. 14), and it is not possible to use the tracing as a reference tracing insofar as the *v* wave is concerned.

The venous tracing in atrial septal defect is usually within normal limits. In many cases the height of the *v* wave approaches that of the *a* wave, or may even be higher (Fig. 8). The high *v* waves are suggestive of tricuspid insufficiency, but in only 2 out of 6 patients with *v* waves higher than *a* waves in atrial septal defect did the surgeon feel a regurgitant flow.

The phlebogram after operation for atrial septal defect presents striking features. The *a* wave is small or absent, and the *y* depression is deeper than the *x* depression (Fig. 15). The *x* depression is only present after the *c* wave. We believe that two main factors are to be considered responsible for this pattern. One factor is that the stroke volume is now significantly smaller in the right heart than before surgery. The dilated right ventricle, which is apt to receive a great stroke output, easily takes up the atrial blood. After the opening of the tricuspid valve the ventricular filling is "rapid" for a long time, and the *y* depression is deep and lasting. During atrial systole the resistance to ventricular filling is still small, as in normal venous tracings when the *a* wave occurs before the end of rapid filling (Fig. 2), and there will be little or no regurgitation into the veins. This factor may be responsible for the small or absent venous *a* wave and the deep *y* depression.

Another factor may be the damage inflicted on the right atrium by the operation, which may cause an absent or small *a* wave and a shallow *x* depression, features imitating atrial fibrillation. This possibility was demonstrated in a patient with atrial septal defect who was operated upon in 1956. At that time we were not yet able to distinguish before operation between the secundum and the primum types of atrial septal defect. At operation the defect proved to be of the primum type, and the surgeon closed the right atrium without further intervention. The venous tracings of this patient presented postoperatively the same features as described above and returned to about normal in half a year (Fig. 16,*A*, *B*, *C*). The curves are strikingly similar to the venous tracings in atrial fibrillation: the *y* depression is deeper than the *x* depression, and the *x* depression is present after the *c* wave, but is absent after the *a* wave.

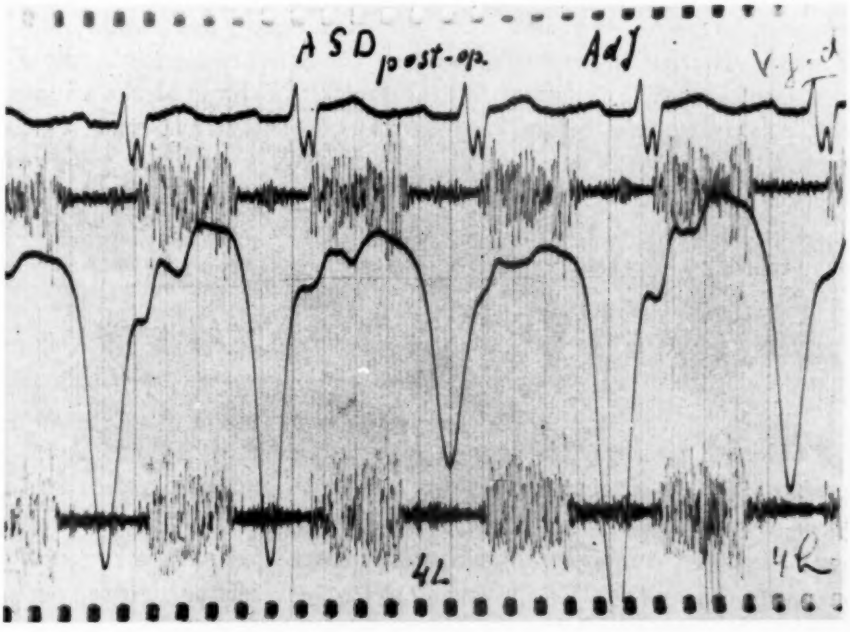

Fig. 17.—Atrial septal defect of the primum type after closure of the defect. In the venous tracing a small *a* wave is present, and the *a*, *c*, and *v* waves merge into one positive wave, indicating tricuspid insufficiency. Compatible with this diagnosis are the pansystolic and mid-diastolic murmurs in the phonocardiogram, recorded at the fourth intercostal space parasternally.

It is also possible that tricuspid insufficiency supervenes after operation for atrial septal defect. The small or absent *a* wave and the absence of the *x* depression after the *c* wave are characteristic of this event (Fig. 17). After operation for ventricular septal defect we observed the same changes in the venous pulse contour as were seen in atrial septal defect. Again the damage to the right atrium by surgery and the changed hemodynamics due to closure of the defect may be the most important factors responsible for these changes in the venous pulse contour. The stroke output of the right heart is less than before operation, and the distensibility of the right ventricle is greater than normal.

SUMMARY

The shape of the venous tracing in various heart diseases is discussed. In tricuspid stenosis the *a* waves are always tall. This is usually also the case in pulmonic stenosis and in high pulmonary arterial pressure. However, in these conditions the *a* waves may be low if they happen to occur in early diastole. This is due to the low resistance to ventricular filling during that phase of the cycle. For an appreciation of the height of the *a* wave it is important, therefore, to take the heart rate into account. With atrial fibrillation the *a* wave is absent, and the *x* depression is only present after the *c* wave, whereas the *y* depression is deeper than the *x* depression. With sinus rhythm and tricuspid insufficiency the *x* depression is present in a normal way after the *a* wave, but it is flattened after the *c* wave and may disappear if the tricuspid insufficiency is severe enough. In atrial fibrillation associated with tricuspid insufficiency the *x* depression may fail to appear. In tricuspid insufficiency there is a deep *y* depression and a distinct early *h* wave, whereas in tricuspid stenosis the *y* depression is shallow and the *h* wave is late or absent. In atrial septal defect the shape of the venous tracing is usually within normal limits, but shows constantly abnormal features after operation. The *a* wave is small or absent, and the *y* depression is deeper than the *x* depression. Possible responsible factors are considered to be the smaller volume of blood entering the dilated right ventricle and the damage inflicted on the right atrium by surgery. Similar postoperative features are seen in ventricular septal defect.

The venous tracing is useful as a reference tracing for the phonocardiogram. It reflects accurately the changes in right atrial pressure, without appreciable delay. Every venous tracing with the *x* depression ending after the second heart sound should be considered suspect as being disturbed by arterial pulsations, and is not reliable as a reference tracing for the phonocardiogram, insofar as the summit of the *v* wave is concerned. The right atrial sound is synchronous with the jugular *a* wave. The opening snap from the right heart is synchronous with the summit of the *v* wave; the opening snap from the left heart often occurs before the summit. The third heart sound from the right heart is synchronous with the *y* depression, whereas the third heart sound from the left heart may be synchronous with the *y* depression or occurs during the descending limb of the *v* wave.

In pulmonary hypertension the distance between the pulmonary component of the second sound and the summit of the *v* wave is greater than in cases in which pulmonary pressure is normal or lower than normal. The mid-diastolic murmurs due to functional tricuspid and mitral insufficiency do not pass the *y* depression; the same applies to the protodiastolic murmur of pulmonary insufficiency in patients with normal or low pulmonary pressure. In contrast, every mid-diastolic murmur that continues distinctly beyond the *y* depression is due to an organic lesion of the tricuspid or mitral orifice.

The author is much indebted to Prof. Dr. H. A. Snellen for his helpful advice and criticism.

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Clinical Evaluation of a New Coronary Vasodilator, 3-Dimethylamino-1,1 2-Tris (4-Methoxyphenyl)-1-Propene Hydrochloride (WIN 5494)

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Recent investigation of a new synthetic series of polymethoxyphenyl amines showed a significant coronary vasodilator action in perfused rabbit heart preparations.[1] This vasodilator action was particularly marked in the compound, 3-dimethylamino-1,1,2-tris (4-methoxyphenyl)-1-propene hydrochloride (WIN 5494). The drug produced an increase in coronary flow during both systole and diastole, and unlike aminophylline, papaverine, and other coronary vasodilators it does not increase the forcefulness of myocardial contraction.[2] It was therefore decided to carry out a controlled study of the clinical value of WIN 5494 as a long-acting coronary vasodilator in patients suffering from angina pectoris.

PATIENTS AND METHODS

Thirteen outpatients from 49 to 70 years of age with well-authenticated and typical features of angina pectoris were studied. There were 9 men and 4 women. In 11 patients the attacks of angina were caused by coronary artery disease, in 1 patient there was associated syphilitic aortitis with aortic regurgitation, and in 1 other patient, a woman aged 60 years, aortic stenosis was present. Three patients had electrocardiographic evidence of past myocardial infarction. All the patients were taking trinitrin tablets freely for their anginal attacks.

A "double-blind" technique was employed in assessing the effect of the drug. An initial control period of 2 months was allowed when the patients were on no additional coronary vasodilator drugs apart from trinitrin. They were then given 1 month's supply of either active WIN 5494 or an identical inert placebo from a paired series of bottles, neither the patient nor the observer being aware of whether active or inert tablets were given. One tablet of 25 mg. was administered four times daily. The patient was also given a specific number of trinitrin tablets. At the end of this first period of 1 month, a further 1 month's supply of the same tablets was given. When this supply was exhausted, a similar procedure was adopted for the following 2 months, the patients receiving the opposite member of the pair. All patients attended the outpatient department at monthly intervals, and at each visit the number of trinitrin tablets consumed in the previous month was checked by the observer, thus ensuring an objective assessment of the number of anginal attacks. In addition, exercise tolerance tests were carried out at the beginning of the study and at monthly intervals at each attendance. These tests were based on Masters' two-step technique, the patient stepping up and down two steps, each being one foot high, and the performance was timed on each occasion until the patient was stopped by either angina or dyspnea. A note was made of the number of circuits the patient could undertake and the total time taken.

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An electrocardiogram was then recorded immediately afterward, using Limb Lead II and Lead V_5 simultaneously. Ischemic changes were indicated by S-T depression of the type and timing described by Wood.[3]

RESULTS

Table I indicates the number of trinitrin tablets taken during the control period and while the patient was on active WIN 5494 and the placebo. In 9 patients, administration of both inert and active tablets was associated with a fall in the consumption of trinitrin, and in 1 patient (No. 13) the number of trinitrin tablets fell to half with the placebo and to a quarter with active WIN 5494. In the remaining 8 patients there was no significant difference in the consumption of trinitrin while on WIN 5494 or the placebo. In 4 patients the number of trinitrin tablets was either the same or increased while on both WIN 5494 and the placebo. The mean consumption of trinitrin over the whole period showed no significant differences between the control period and the period during which the patients were on either WIN 5494 or the placebo.

TABLE I. CONSUMPTION OF TRINITRIN TABLETS DURING CONTROL PERIOD AND WHILE THE PATIENT WAS ON PLACEBO, WIN 5494, AND PERITRATE

PATIENT NUMBER	AGE (YR.)	SEX	DURATION OF ANGINA (YR.)	NUMBER OF TRINITRIN TABLETS PER WEEK		
				CONTROL PERIOD	PLACEBO	WIN 5494
1.	50	M	—	6	3	5
2.	58	M	13	60	46	35
3.	60	F	8	10	13	11
4.	61	M	3	4	1	1
5.	51	M	3	13	17	18
6.	70	M	2	16	9	10
7.	58	M	—	6	9	6
8.	60	F	5	9	1	3
9.	52	F	3	7	4	3
10.	65	M	9	5	7	4
11.	58	M	2	3	3	3
12.	49	M	1	23	16	15
13.	64	F	10	22	11	5
	Mean			13.7	9.2	9.1
	Standard Error			4.5	3.9	2.7

Side effects with WIN 5494 were minimal, and only 2 patients complained of minor gastrointestinal discomfort.

The results of the two-step exercise tolerance tests are shown in Table II. The mean number of circuits undertaken while the patient was on the placebo was greater than during the control period, but the difference was not a significant one ($p > 0.05$). Similarly, there was no significant change with WIN 5494. There was also a reduction in the mean time taken to complete one circuit over the whole series with both WIN 5494 and the placebo, but again the differences were

not significant ones. Table III shows that ischemic changes in the electrocardiogram after the patient had exercised were present in 7 patients in the series during the control period (Fig. 1), and in only 1 of these 7 patients was any objective improvement produced by WIN 5494 (Fig. 2). In 1 other patient, ischemic changes were present during the control period and disappeared while the patient was on both active and inert tablets. In the remaining 5 patients the ischemic changes after exercise persisted throughout the study.

TABLE II. RESULTS OF EXERCISE TOLERANCE TESTS

PATIENT NUMBER	TOTAL NUMBER OF CIRCUITS			MEAN TIME PER CIRCUIT (SEC.)			CAUSE OF STOPPING		
	CONTROL PERIOD	PLACEBO	WIN 5494	CONTROL PERIOD	PLACEBO	WIN 5494	CONTROL PERIOD	PLACEBO	WIN 5494
1.	32	41	35	4.4	3.9	4.0	D	A	A
2.	27	21	25	3.3	3.1	3.5	A	D	A
3.	14	23	18	3.8	3.3	4.0	D	D	A
4.	26	33	39	4.8	4.1	4.0	D	D	D
5.	31	47	42	2.7	2.5	2.7	A	A	A
6.	27	100	—	3.5	2.1	—	D	D	—
7.	64	46	30	4.0	3.6	3.0	A	A	A
8.	21	18	24	6.4	5.0	5.2	D	D	A
9.	16	20	19	4.0	2.8	2.9	D	A	A
10.	35	46	45	3.0	2.6	2.4	A	A	A
11.	21	21	14	3.1	2.9	2.9	A	D	A
12.	16	19	18	4.0	3.8	3.7	A	A	A
13.	9	16	18	8.3	1.5	3.0	A	A	A
Mean	26.1	34.7	27.3	4.3	3.2	3.4			
Standard Error	3.5	6.2	2.4	0.4	0.3	0.4			

A: Angina pectoris. D: Dyspnea.

TABLE III. PROGRESS OF ISCHEMIC CHANGES IN THE ELECTROCARDIOGRAM DURING THE STUDY

PATIENT NUMBER	PRESENCE OF ISCHEMIC CHANGES		
	CONTROL PERIOD	PLACEBO	WIN 5494
1.	0	0	0
2.	++	++	++
3.	0	0	+
4.	0	0	0
5.	+	+	+
6.	0	0	−
7.	+	+	+
8.	0	0	0
9.	0	0	0
10.	+	+	+
11.	+	0	0
12.	+	+	0
13.	+	+	+

In 1 patient with particularly severe and frequent angina (Patient No. 2), the dose of WIN 5494 was increased to 50 mg. four times daily. Dizziness, slight confusion, and visual disturbances of a migrainous character occurred. They were relieved by withdrawing the drug. There was no change in pulse rate, blood pressure, or weight of the patients during the course of the investigation.

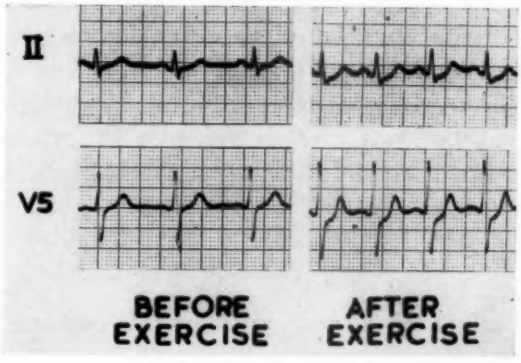

Fig. 1.—Electrocardiogram showing ischemic changes following exercise.

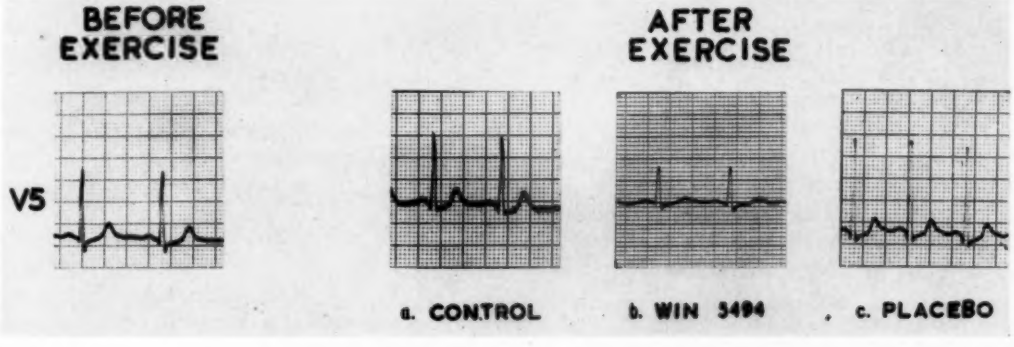

Fig. 2.—Electrocardiogram in Patient No. 11 showing improvement in the ischemic pattern after exercise while the patient was on WIN 5494 but not during administration of placebo.

DISCUSSION

It has been stated that in the administration of any antianginal drug the therapeutic effect is directly related to the personality of the physician and his own belief in the curative powers of the drug, together with the susceptibility of the patient and the intensity of the patient's desire to be cured.[4] This view is supported by Cole, Kaye and Griffiths,[5] who studied the effect of four coronary vasodilators in cases of angina pectoris and found a decrease in the frequency of chest pain in every patient, regardless of whether an active drug or placebo was being administered. The importance of a "double-blind" technique in the investigation of an antianginal agent is therefore plain. More important still is the objective index of improvement provided by the electrocardiogram during a standard exercise tolerance test.

A number of unpublished clinical observations in which WIN 5494 has been tried in a total of 40 patients with varying degrees of angina indicated that the results were favorable (Russek, Korry, Rike, Altman, Schwedel, Rubin and Mullin, 1958 and 1959). In these 40 patients the results were considered excellent in 13, good in 24, and bad in only 3 patients. However, the response was assessed subjectively on the consumption of trinitrin and apparently without a "double-blind" technique. In the present study an initial decrease in the consumption of trinitrin occurred in the majority of patients, irrespective of administration of either WIN 5494 or the placebo. The experience of Cole and associates (1959) was similar. No significant differences were found, however, between WIN 5494 and the placebo, and there was also no evidence of improvement with either drug in the rate of exercise or total amount of exercise possible in carefully controlled exercise tolerance tests.

SUMMARY

1. The clinical effect of a new coronary vasodilator, 3-dimethylamino-1,1,2-tris (4-methoxyphenyl)-1-propene hydrochloride (WIN 5494) has been studied in 13 patients with angina pectoris, using a "double-blind" technique.

2. No significant change in either the consumption of trinitrin or in exercise tolerance tests followed administration of the drug in a dose of 25 mg. four times daily.

3. The importance of a controlled study and objective criteria of improvement in the assessment of an antianginal drug is pointed out.

The author is indebted to Dr. David Verel for his helpful critisicm and to Miss G. Kipling and the electrocardiographic technicians of the Sheffield Region Cardiovascular Centre for their willing cooperation in this study. I would also like to thank Dr. K. Boheimer of Bayer Products Ltd. for the supply of WIN 5494 and placebo.

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Experimental and Laboratory Reports

Pendulum Type of Artificial Heart Within the Chest: Preliminary Report

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In the artificial heart described in this paper the ventricles empty alternately rather than simultaneously. It is our aim to construct a pump that can replace permanently the irreparably sick human heart. Experimental studies in the construction of valves, ventricles, and artificial vessels led to the adoption of polyurethane VC[1-6] to minimize clotting and hemolysis. Cahill,[7,8] in our laboratory, found that a pump that incompletely empties the ventricles, and that contains polyurethane valves of our design caused less hemolysis than any other pump now available. Simultaneously, work proceeded on designs of the driving mechanism for these pumps.

Before the large investments required to build a durable pump were justified, preliminary studies had to be done to determine the most promising approach. One of our pumps uses five solenoids to displace oil, which in turn compresses two ventricles.[1,2] Another uses a roller which gently compresses the ventricles; it is described in another article.[9] The preliminary model described in this paper alternately compresses the right and left polyurethane ventricles. It seemed promising enough to serve as a model for a more durable pump, which is under construction.†

REQUIREMENTS FOR AN ARTIFICIAL HEART

A permanent mechanical replacement for the human heart requires the following: (1) a small, double pump (right heart and left heart); (2) variable rates (between 60 and 160 strokes per minute); (3) variable output (between 1.5 and at least 5 liters per minute for each side); (4) input pressure or atrial pressure of no more than 16 mm. Hg and no less than 0 mm. Hg (in other words, the pump should not suck hard when the blood available is insufficient to fill the atrium); (5) out-

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put pressure of the right ventricle of at least 20 mm. Hg, but 80 mm. Hg may be required, and output pressure of the left ventricle of at least 120 mm. Hg, but 180 mm. Hg may be required; (6) 24-hour output of the left side equal to that of the right side (assuming that no blood is pooled in either the greater or the lesser circulation, this can be obtained if the filling of each atrium determines the output of the corresponding ventricle); (7) a diastole long enough to allow filling of the ventricle, although it is not absolutely necessary that the atria contract (according to Wiggers,[10] in both man and dogs, diastole lasts 53/100 second, whereas systole lasts 27/100 second, and maximal ejection of the ventricle takes only 9/100 to 12/100 second); (8) source of energy: (a) a battery with a charger outside the body for direct-current motors or solenoids, (b) or an alternating power supply for alternating current motors (both *a* and *b* require wires from the power supply into the chest), (c) or a small atomic power plant inside the chest; (9) dissipation of heat (the heat formed by the motors will best be transmitted to the blood for radiation by the skin and lungs); (10) ease of insertion and ease of replacement.

PUMP DESIGN

By requiring only one ventricle to empty at a time, we can use a smaller pump and divide the work load of the electric motor more evenly. There is no apparent reason why pulsations alternating between greater and lesser circulations should not be acceptable to an organism, provided the volumes pumped by the right and left sides over a certain period of time are equal.

The pump employs a small motor, either a General Electric direct-current motor* or a Globe alternating-current motor.† Each of these motors has a gear-reduction system, which reduces the shaft rotation to approximately 110 r.p.m. The motor, suspended by pivots, swings back and forth within a rigid housing. The swing is caused by an eccentric and a ball-bearing lever arm fixed to one side of the housing (Figs. 1 and 2). As it is driven back and forth, the body of the motor alternately compresses each ventricle against the housing, thereby expelling its contents. Ventricles and valves are made of polyurethane (Fig. 2,*B*), as are the connecting tubes which anastomose with living vessels.

RESULTS

Tests in Mock Circulation.—The first model was built around the inexpensive General Electric motor. It pumped as much as 1,800 ml. per minute from each ventricle when pumping in a mock circulation[11] at rates of from 88 to 106 strokes per minute against a diastolic pressure of 100 cm. H_2O on the systemic side and 25 cm. H_2O on the pulmonary side. The output varied in direct linear relation to the filling pressure of the left atrium (Fig. 3). With a left atrial pressure of 15 cm. H_2O, it pumped 1,800 ml. per minute; but when the left atrial pressure was reduced to 0 cm. H_2O, it pumped less than 600 ml. per minute.

Since the walls of the ventricles are fixed neither to the wall of the housing nor to the motor, but lie loose in the space provided, no suction takes place if the walls of the ventricles are thin and flexible. As long as some blood is available in the atrium, no negative pressure develops. In this it mimics the natural heart.

Since the atrial pressure determines filling of the ventricle, and this, in turn, determines the output of the ventricle, a self-regulating mechanism is established. If one side were to pump more than the other, increased atrial pressure on the second side would produce a higher output and bring the pressures on both sides

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*General Electric motor No. 5BA10AJ18D, 27 VDC, developing 12 ounce-inches of torque at 110 r.p.m.

†Globe motor No. AC20884, 115 VAC, single-phase, 60-cycle, developing 1.2 ounce-inches of torque at 120 r.p.m. (rate: 128 without load).

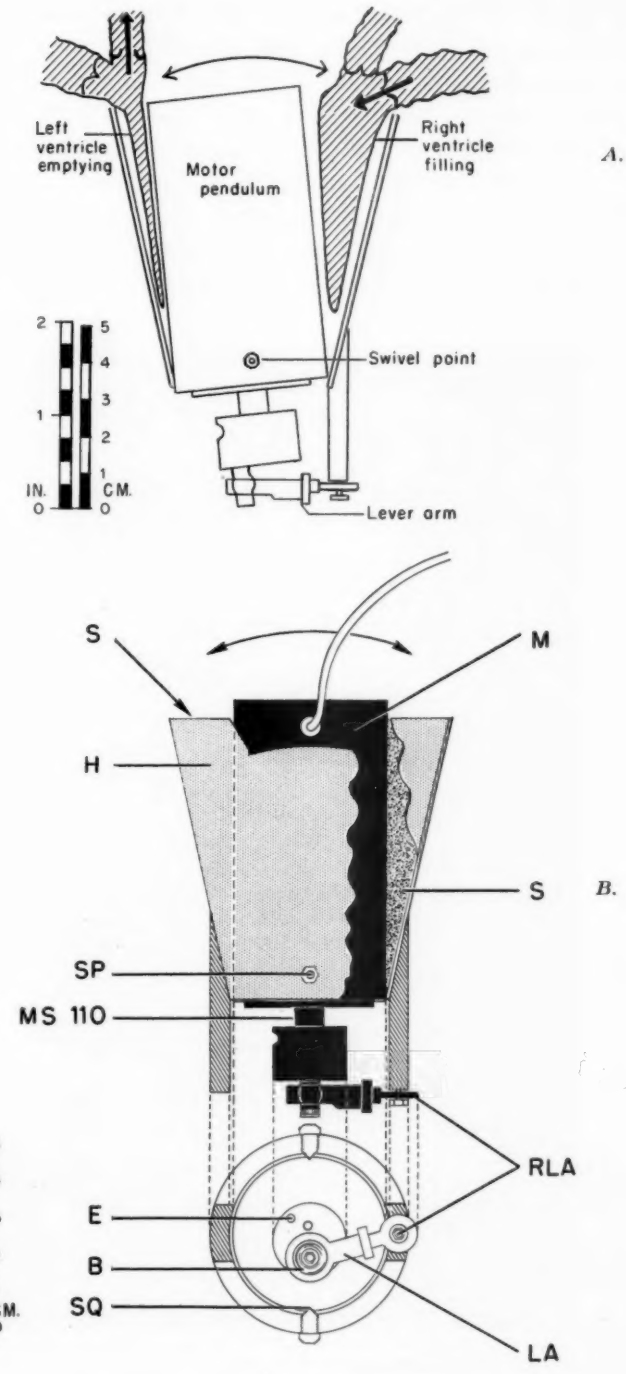
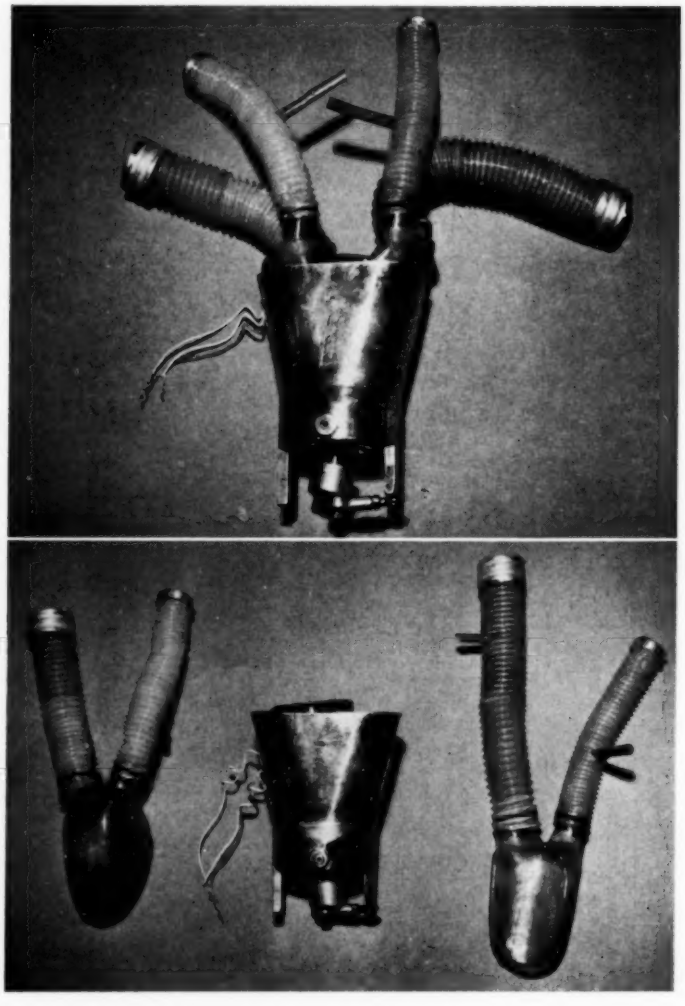


Fig. 1.—*A*, Diagram of pendulum pump. The ventricles are located on either side of the motor. When the motor swings, the ventricles are compressed alternately. *B*, Diagram of hardware of pendulum pump. *SP*, Swivel point. *LA*, Lever arm, adjustable. *B*, Ball joint, mounted on *E*, eccentric holes. *RLA*, Rotation point for lever arm on housing, allowing some up and down movement as well. *MS 110*, Motor shaft, 110 r.p.m. *H*, Housing. *M*, Motor. *S*, Space between housing and motor allowing for one ventricle on either side.

to equilibrium again. When the left and right circulations were crossed over in the mock circulation, as they are in life, equilibrium was quickly established and was maintained for the duration of the test.

To test the pump for hemolysis, human blood which had been used that morning in an extracorporeal heart-lung machine was pumped for 3 hours in a mock circulation and the increase in free hemoglobin in the plasma was determined.[7] The systemic circulation showed an increase in free hemoglobin in the plasma of 30 mg./100 ml. per hour, whereas the pulmonary circuit showed an increase of 15 mg./100 ml. per hour (Fig. 4).



A.

B.

Fig. 2.—*A* and *B*, Globe motor pendulum pump. The ventricles, valves, atria, aorta, and pulmonary artery are made of Polyurethane VC. Atria, pulmonary artery, and aorta are corrugated to allow flection without kinking.

No significant heat developed in the motor. The sides of the motor are in close contact with the two ventricles, so that any heat formed may be mediated to the blood through the thin walls of the ventricles.

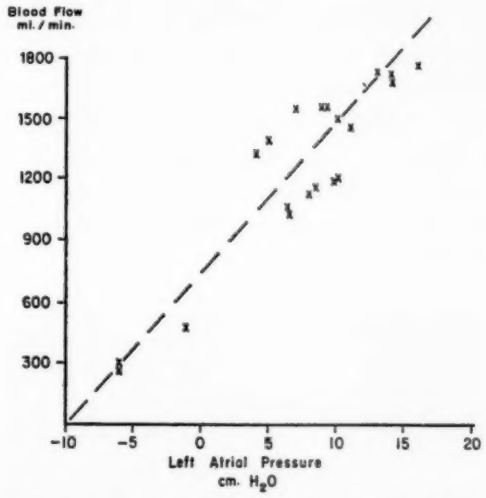


Fig. 3.—Left ventricular output of pendulum heart in relation to various left atrial pressures while the artificial heart is pumping in a mock circulation: aortic pressure, 100 cm. H_2O; pulmonary artery, 17 cm. H_2O; right atrium, 5 to 18 cm. H_2O; rate, 100 strokes per minute. Ventricular output has a direct linear relation to atrial pressure. In the mock circulation it is possible to make the left atrial pressure negative. This will not happen in vivo as long as 600 ml. of blood per minute (for this pump) is available in the atrium.

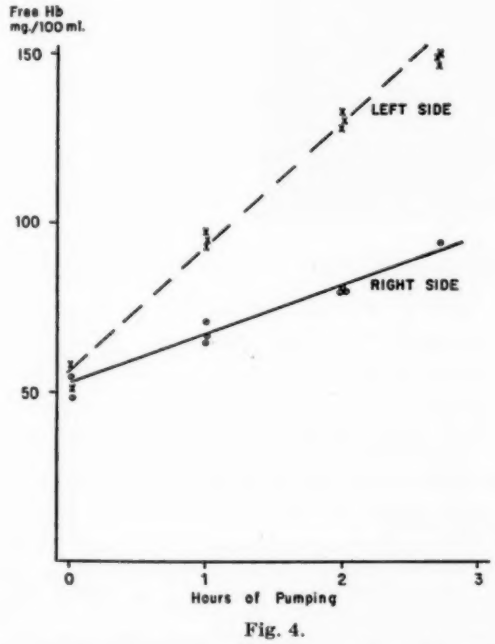


Fig. 4.

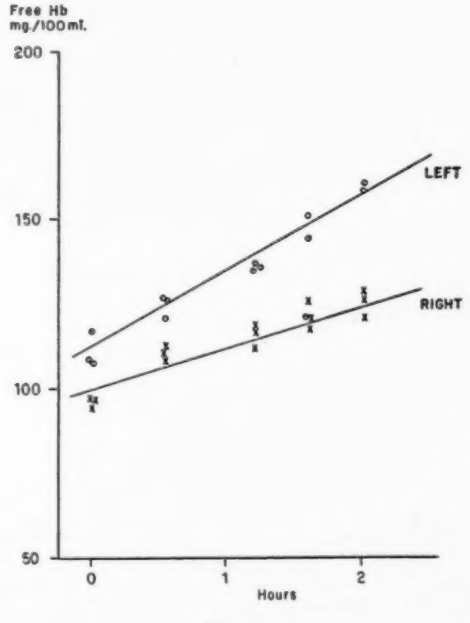


Fig. 5.

Fig. 4.—Rate of formation of free hemoglobin with pendulum pump (General Electric motor). The concentration of free hemoglobin increased 30 mg./100 ml./hr. in the systemic circuit and 15 mg./100 ml./hr. in the pulmonary circuit when human blood was pumped in the mock circulation.

Fig. 5.—Rate of formation of free hemoglobin with pendulum pump (Globe motor). The concentration of free hemoglobin increased 25 mg./100 ml./hr. in the systemic circuit and 12 mg./100 ml./hr. in the pulmonary circulation when human blood was pumped in the mock circulation. The experiment was performed at room temperature. On the systemic side, the flow was 1,060 ml./min., against an aortic diastolic pressure of 100 cm. of blood; on the pulmonary side, the flow was not measured, but was estimated to be of the same magnitude, against a diastolic pulmonary pressure of 25 cm. of blood. Dow Corning Antifoam A,* painted on the inside of the mock circulation, prevented foaming.

*Dow Corning Corporation, Midland, Mich.

These tests were sufficiently encouraging to justify building a housing for the more expensive Globe alternating-current motor. An alternating-current motor has the advantage of longer life because it has no brushes. The planetary gears in the Globe motors also have a longer life than do the gears in the General Electric motor. Flow tests were encouraging. A test for hemolysis showed an increase of free hemoglobin in the plasma of 25 mg./100 ml. per hour on the left side and of 12 mg./100 ml. per hour on the right side (Fig. 5). No appreciable heat developed during the 3-hour run.

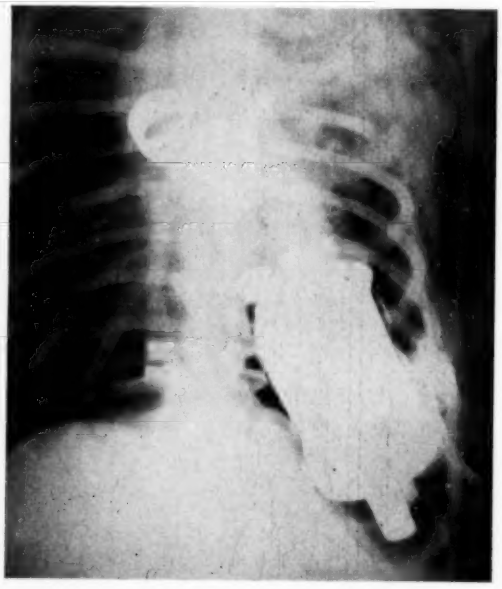


Fig. 6.—Roentgenogram of chest with artificial heart replacing the dog's heart. No pulmonary edema.

TABLE I. RECORD OF EXPERIMENT, JUNE 26, 1959 (DOG, 30.2 KG.)

TIME	REMARKS
9:42	Incision made. Venous pressure 6 cm. H_2O; mean arterial pressure 138 mm. Hg
10:06	Chest opened
10:53	Started on pump-oxygenator; vessels being occluded
11:11	Heart removed; anastomoses commenced
12:27	Artificial heart started. Venous pressure 4.5 cm. H_2O; mean arterial pressure 84 mm. Hg
12:37	Pump-oxygenator discontinued; animal on his own. Venous pressure 3 cm. H_2O; mean arterial pressure 90 mm. Hg
12:45	Pressure tracings made. Venous pressure 12 cm. H_2O; mean arterial pressure 40-45 mm. Hg. Arterenol started*
1:15	Pressure tracings made. Venous pressure 15 cm. H_2O; mean arterial pressure 154 mm. Hg
3:30	Chest closed; animal breathing on his own. Corneal, wink, and tendon reflexes good. Venous pressure 15 cm. H_2O; mean arterial pressure 160 mm. Hg
5:30	Blood pressure falling; reflexes disappearing
5:50	Experiment terminated

***Levarterenol bitartrate was administered when the mean arterial pressure fell below 80 mm. Hg. It was required for 36 minutes in the first 3¾ hours, and longer during the last 1½ hours of the experiment.**

Animal Experiment.—On June 26, 1959, the Globe motor pump was placed in the chest of a 30-kilogram dog through a left thoracotomy. During removal of the natural heart and insertion of the artificial heart, the circulation was sustained by a Björk oxygenator and pump. A brief record of this experiment is shown in Table I. The lever arm of the pump was adjusted for a maximum output of 1,000 ml. per minute from each ventricle, which for a 30-kilogram dog is not adequate, and which may explain why levarterenol bitartrate (Levophed*) was needed at times. The animal breathed spontaneously for 2 hours after the chest was closed, maintained corneal, wink, and tendon reflexes, and for more than 5 hours maintained a mean blood pressure above 80 mm. Hg.

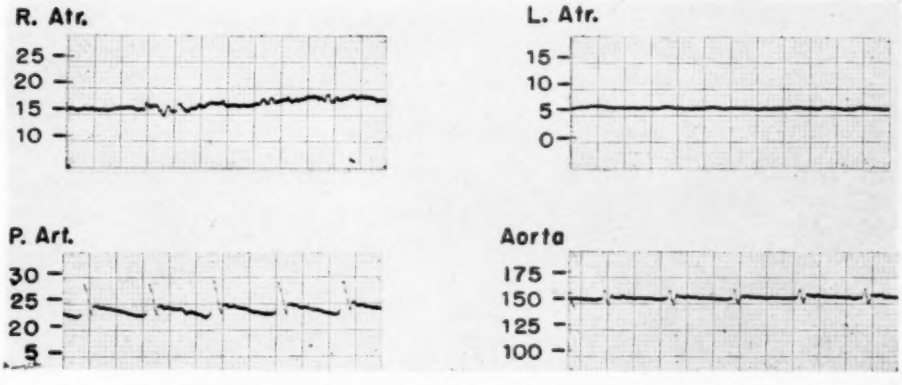


Fig. 7.—Pressure tracings from a dog with circulation maintained with pendulum artificial heart inside closed chest. Arterenol was given during the recording. Recordings were made on a single-channel Sanborn recorder through a Statham transducer No. 1141 P23Db.

An intravenous infusion of arterenol was needed for 36 minutes during the first 3¾ hours of the experiment; thereafter, additional arterenol was needed. The maximum mean arterial pressure obtained while the animal was given arterenol was 200 mm. Hg. The color of the mucous membranes suggested excellent oxygenation; no serious technical problems were encountered, and although the animal's blood was fully heparinized, there was no excessive bleeding. The experiment was terminated after 5⅓ hours. No pulmonary edema was evident in a roentgenogram of the chest made after 5 hours (Fig. 6), nor was it present at necropsy.

Pressure tracings were made during this experiment by inserting 21-gauge needles into the polyurethane connecting tubes. Mean pressures in the aorta, pulmonary artery, and left and right atria were 150, 25, 5, and 17 mm. Hg, respectively (Fig. 7).

SUMMARY

In an artificial heart the right and left ventricles need not contract simultaneously. A pendulum type of mechanical heart is described in which a small

*Winthrop Laboratories.

motor swings on pivots within a rigid housing, compressing each ventricle alternately. The output may be as high as 1,800 ml. per minute, and is directly related to atrial pressure. Hemolysis is acceptably low. With one of these pumps an anesthetized dog maintained blood pressure, spontaneous respiration, and corneal, wink, and tendon reflexes for 5 hours. While the mechanical heart sustained the animal's circulation, the following mean pressures were recorded: aorta, 150; pulmonary artery, 25; left atrium, 5; and right atrium, 17 mm. Hg.

We are indebted to Mr. Howard Abrams and to Mr. Nate Leiptz of Curtis Industries, Inc., Cleveland, Ohio, for their assistance in constructing these pumps.

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Roller Type of Artificial Heart Within the Chest: Preliminary Report

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Cleveland, Ohio

The roller type of artificial heart described here has the advantage of a long diastole, which facilitates filling of the ventricles. As in the pendulum type of artificial heart, described in another article,[1] the ventricles empty alternately rather than simultaneously. This is the third preliminary report[1-3] in which possibilities are explored to design artificial hearts to replace the irreparably sick human heart.

PUMP DESIGN

The pump described here (Fig. 1) derives its power from a Globe DC motor.†‡ A small, freely moving roller rotates within a larger brass housing in which are two polyurethane ventricles. These ventricles are 2 mm. deep and 25 mm. wide and lie against the outer housing, with ports through the housing to permit entry of the atria and exit of the aorta and the pulmonary artery. Between the ventricle and the outer housing is a sheet of polyurethane foam, so that the rotating roller compresses the ventricles against a somewhat yielding surface, thereby minimizing trauma to red blood cells. Only one valve for each ventricle is needed in this type of pump. These valves are of the tricuspid, semilunar type,[4] and are placed in the exit ports (aorta and pulmonary artery). The vessels extend beyond the outer housing in order to facilitate anastomosis to living vessels.

RESULTS

Tests in Mock Circulation.—The roller-pump artificial heart was tested in a mock circulation.[5] The output of each ventricle varied with atrial pressure. As the left atrial pressure in the mock circulation was increased from −5 to +25 cm. H_2O, the left ventricular flow increased from 200 to 2,200 ml. per minute

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†DC Motor No. 5A545-1—24 volts; planetary gear reduction; revolution of main shaft: 110 r.p.m. Globe Industries, Inc., Dayton, Ohio.

‡Mr. Norman Dann, Designers for Industry, Inc., Cleveland, Ohio, suggested to us the use of a Globe motor in the center of the roller pump.

(Fig. 2). A similar curve was obtained for the right atrial pressure and the right ventricular output. Since the filling of the ventricles, and, consequently, their outputs are determined by the atrial pressures, a self-regulating mechanism is established. If one side pumps more than the other, the resultant increased venous pressure on the other side must lead to an increased output by that side.

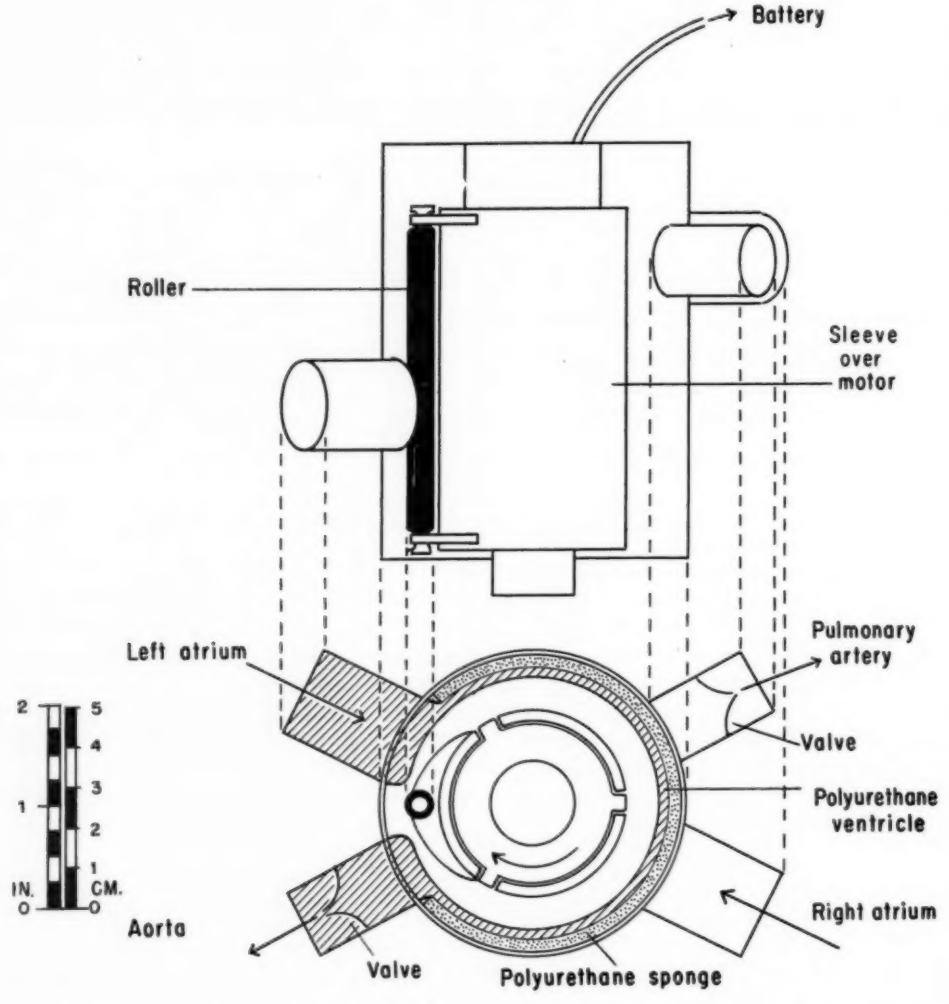

Fig. 1.—Diagram of a roller type of artificial heart. *Below*, A cross section through one of the shallow ventricles. No mitral or tricuspid valve is necessary, and there is an open communication between the atrium and the ventricle until it is closed off by the roller. While the roller proceeds and compresses the ventricle against the polyurethane sponge, it propels the blood in front of it until pressure begins to build up in the last part of the ventricle. Only when the pressure exceeds the existing pressure in the aorta will the aortic valve open. The length of systole depends upon the amount of blood in the ventricle, and upon the volume and distensibility of the outflow part of the ventricle. Diastole lasts the entire cycle, with the exception of the short period during which the roller actually occludes the open communication between the atrium and the ventricle.

In a mock circulation,[5] pressure tracings from both atria and from the aorta and pulmonary artery were taken with a Sanborn single-channel recorder. A slightly negative pressure developed in the atrium when there was not enough

fluid to fill the ventricle. This negative pressure depended upon the thickness of the walls of the ventricle and upon the tendency of the ventricle to re-expand after having been compressed.

The pump was tested to determine the amount of hemolysis it caused, using three pints of human blood that had been used earlier that day in a pump-oxygenator.[6] Samples of blood for determination of the concentration of free hemoglobin in the plasma were obtained with the blood at room temperature. The concentration of free hemoglobin in the plasma increased at a rate of 30 mg./100 ml. per hour (Fig. 3), and was essentially the same for the greater and the lesser circulations. It may be remembered that recirculation of blood without an animal in the circuit is a severe test.

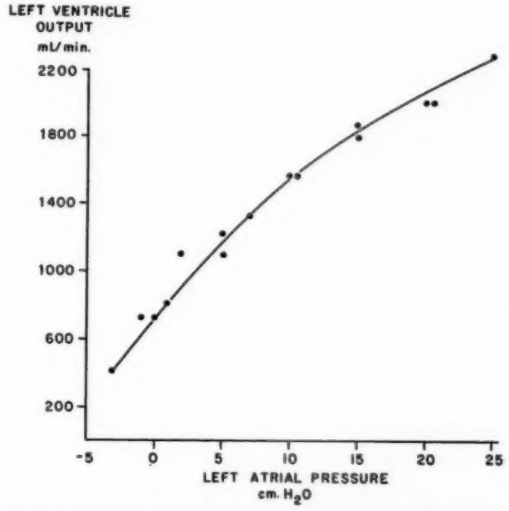

Fig. 2.—Relation of left atrial pressure to left ventricular output in the roller pump. When the left atrial pressure is increased from −5 to +25 cm. H_2O, the left ventricular output increases from 200 to 2,200 ml./min. The test was done in the mock circulation against a simulated aortic diastolic pressure of 83 cm. H_2O, a pulmonary arterial pressure of 15 cm. H_2O, and a constant right atrial pressure of 5 cm. H_2O.

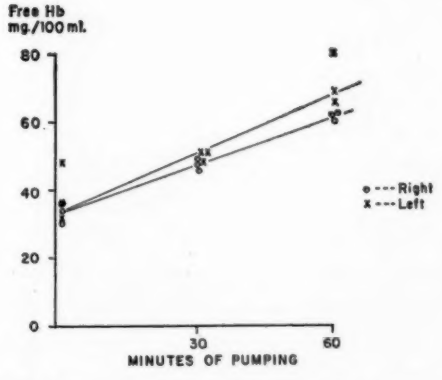

Fig. 3.—Hemolysis caused by the roller type of pump. The increase of free hemoglobin in the plasma during recirculation of 1,500 ml. of human blood in the mock circulation with the roller pump, at a flow rate of 1,100 ml./min. at an aortic diastolic pressure of 100 cm. blood, pulmonary arterial pressure of 18 cm. blood, right atrial pressure of 9 to 14 cm. blood, left atrial pressure of 7 to 10 cm. blood, and pumping rate of approximately 100 strokes/min. The concentration of free hemoglobin increases at almost the same rate on right and left sides, approximately 30 mg./100 ml./hr.

Animal Experiment.—On June 29, 1959, an experiment was done using a 24.8-kilogram dog anesthetized with pentobarbital. The dog's natural heart was removed, and the artificial heart was connected to the dog's circulation. Because outlet ports of the mechanical heart were not sufficiently streamlined to fit inside the chest, the chest wall could not be closed. The operation was completed in 55 minutes, while the circulation was maintained with a Björk oxygenator and Sigmamotor pumps.

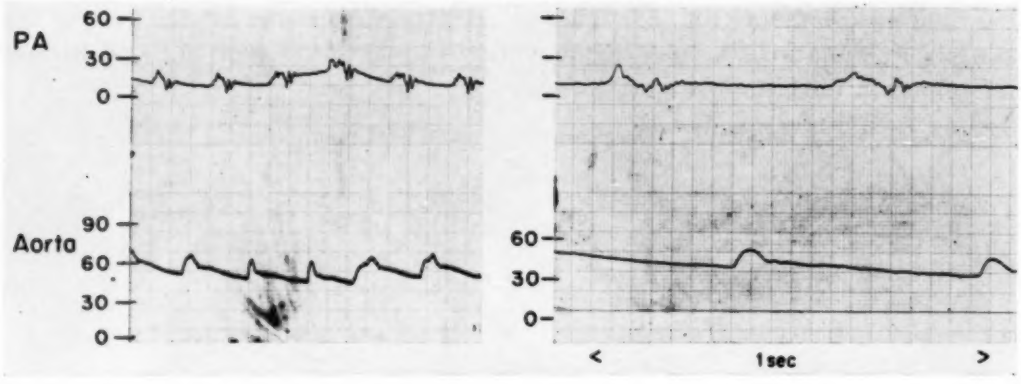

Fig. 4.—Simultaneous recording of pressures in pulmonary artery (*above*) and in aorta (*below*) during maintenance of the circulation with the roller pump in a 24.8-kilogram dog. Sanborn multichannel recorder; 20-gauge, 1½-inch needle; Statham gauge P23Db (*above*) and P23D (*below*). Note the relatively short duration of the pressure waves in the aorta and pulmonary artery. The waves in the pulmonary artery are no longer than 20/100 sec., and the last part of the wave is due to rebound and inertia. Also note the alternation between pulmonary and aortic pressure waves, which is seen most clearly in the high-speed recording.

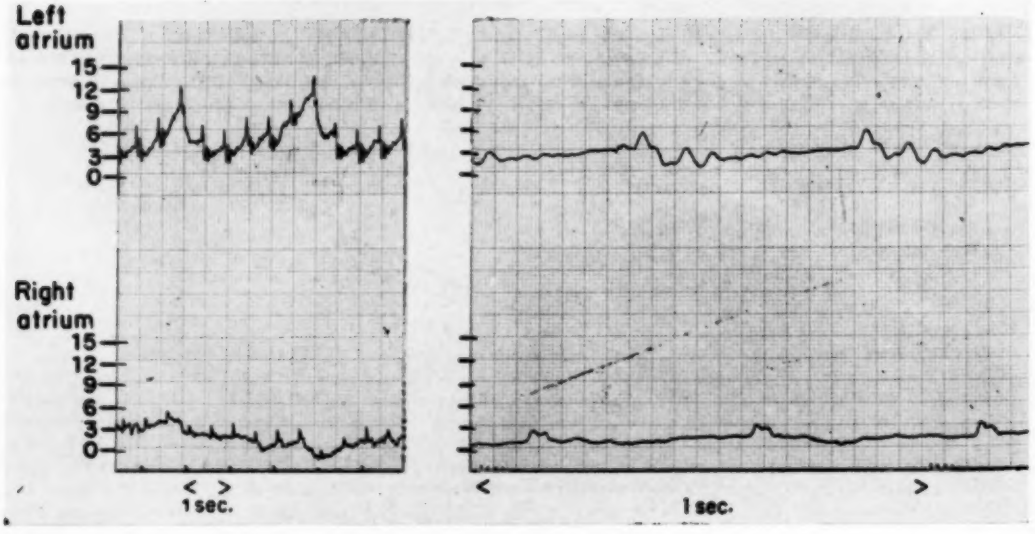

Fig. 5.—Simultaneous recording of left (*above*) and right (*below*) atrial pressures. Respiratory changes in the left atrial pressure are evident in the upper tracing. The moment at which the roller passes the opening between the atrium and the ventricle is indicated by shallow waves. Note the alternation of these waves in the left and the right atria. The filling period of the atria is long. It excludes, at most, the short wavy period of 15/100 sec. from the total duration of the stroke, which in this case is 50/100 sec.

A mean arterial pressure of about 60 mm. Hg was maintained without the administration of pressor agents. Corneal, wink, and tendon reflexes were noticed, and although the chest was not closed, indications of spontaneous respiration were observed. Oxygenation as judged by the appearance of the tongue and the color of the blood was excellent.

In order to observe vascular responses while the dog's circulation was maintained by the roller pump, some drugs were given intravenously. The maximal arterial pressure obtained with levarterenol bitartrate (Levophed*) was 220 mm. Hg, and with pentolinium tartrate (Ansolysen†) a decrease to 30 mm. Hg was brought about.

The experiment was terminated 2 hours after the artificial heart was put in place. No pulmonary edema was observed at necropsy.

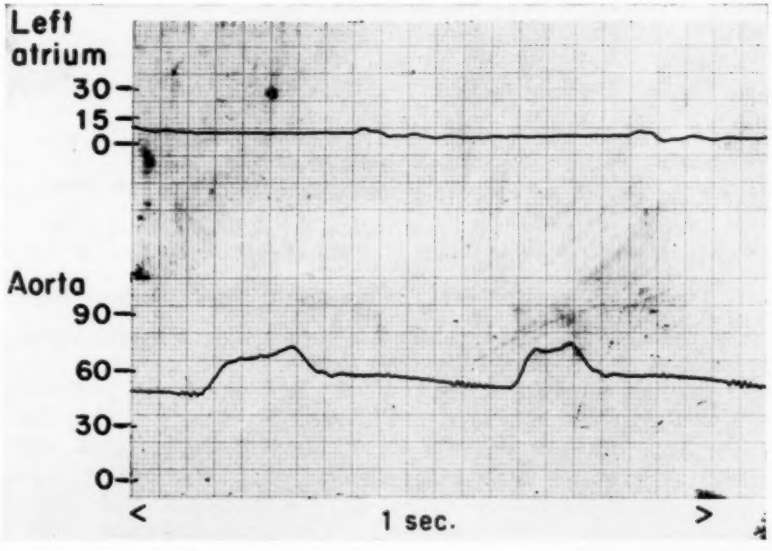

Fig. 6.—Simultaneous recording of left atrial pressure (*above*) and aortic pressure (*below*). The roller passes the opening between the left atrium and the ventricle shortly after having completed the expulsion of the blood from the left ventricle. Notice the relatively brief period of emptying of the ventricle, followed by a gradual decrease in pressure in the aorta until the next stroke hits.

Pressure tracings were made during the experiment by inserting 20-gauge needles attached to a Statham transducer on a multichannel Sanborn recorder. Pressures in the aorta, the pulmonary artery, and the right and left atria were 75/51, 25/3, 3/1, and 6/2 mm. Hg, respectively. Alternating pressure waves were observed in the pulmonary artery and aorta (Figs. 4, 5, and 6). The low and even atrial pressure tracings, indicating an almost continuous filling of the ventricles, were only briefly interrupted by a short wave when the roller passed the port of entry.

During the experiment the free hemoglobin concentration of the blood plasma of the dog decreased from 434 to 346 mg./100 ml. within 30 minutes,

*Winthrop Laboratories.
†Wyeth Laboratories.

indicating that the excessive hemoglobin content caused by the use of "sucker blood" early in the experiment was gradually eliminated (by the reticuloendothelial system), and that no increase occurred on account of the roller pump.

SUMMARY

The roller type of artificial heart has the advantages of (1) only one valve for each side (the aortic and pulmonary artery valves), (2) a favorable relation between filling pressure and output, so that the pressure in each atrium determines, to a large extent, the ventricular output on the same side, and (3) a long filling period for the ventricles. The roller type of artificial heart is basically of simple design. It must be streamlined to fit into the chest. This pump maintained the circulation of a dog for 2 hours. Pressure tracings showed the alternation between pulmonary arterial and aortic pressures, and the long filling period (diastole) for the ventricles.

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Measurements of Unipolar Potentials in the Electrical Field Produced by an Arbitrary Dipole in the Elliptical Homogeneous Lamina

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It is the purpose of this article to present the method by which the weighted central terminal may be developed for the elliptical homogeneous conducting lamina which contains the arbitrary electrical dipole. The weighted central terminal may then be used as an entirely satisfactory reference potential in making measurements of unipolar potentials.

METHOD

Theory.—The method is basically similar to that recently reported[1,2] for making accurate measurements of unipolar potentials in the circular homogeneous lamina. In the case of the elliptical lamina under discussion, the appropriate reference potential V_{TW} is that of the weighted central terminal which has the average value of weighted potentials from 72 electrodes on the boundary of the ellipse (Fig. 1). We suppose the conductor is in the XZ plane, and take the major axis of the ellipse along the axis of X and the minor axis of the ellipse along the axis of Z. The positions of the 72 boundary electrodes are determined by the magnitude of the central angle Φ taken in steps of 5° from where $\Phi = 0$ on the positive axis of X and moving counterclockwise through $\Phi = 90°$ on the positive axis of Z and on through 355°. The appropriate values of the resistors which connect the 72 boundary electrodes to the weighted central terminal are determined by making the magnitude of the resistors inversely proportional to the *areas* of the 72 sectors determined by the central angle Φ taken in steps of 5° from where $\Phi = 2.5°$ to where $\Phi = 357.5°$. This arrangement places each boundary electrode at the "midpoint" of the boundary of any given sector. In this way the weighted central terminal averages the potentials that would occur at the 72 electrodes on the circumference of a homogeneous circular lamina with an effective radius equal to that of the hemimajor axis of the ellipse. The areas of the sectors of the ellipse are computed by the formula

$$A = \frac{ab}{2} \int_{\beta}^{\alpha} \frac{d\Phi}{\frac{b}{a}\cos^2 \Phi + \frac{a}{b}\sin^2 \Phi} \tag{1}$$

where A is the area of the sector, a is the hemimajor axis, b is the hemiminor axis, and Φ is the central angle from the limits $\Phi = \beta$ to $\Phi = \alpha$.

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All together 19 computations are required for any given ellipse, since there are 17 full sectors and 2 half sectors in one quadrant of the ellipse. The sum of the sectors thus determined for one quadrant can be multipled by 4 and compared with πab, the total area of the ellipse. The resistor on the electrode $\Phi = 0°$ is arbitrarily taken as 1.000 megohms, and the remaining resistors are made inversely proportional to the areas of the remaining sectors (see discussion). The set of 72 resistors thus determined will be constant for any given ellipse for all arbitrary positions of the dipole. The resistor values were rounded off through the nearest 1,000 ohms, and the high tolerance of 0.1 per cent was obtained from the Allen-Bradley Co. The particular ellipse chosen was the Frank[3] ellipse, where $a/b = 1.32$.

TABLE I. BOUNDARY POTENTIALS USING THE NELSON FORMULA AND THE FRANK ELLIPSE WITH DIPOLE 13*

Φ	RESIST.	POT. V_s	POT. V'_s	Φ	RESIST.	POT. V_s	POT. V'_s
0°	1.000	2.39683	2.39683	180°	1.000	−1.99782	−1.99782
5°	1.015	2.27764	2.24398	185°	1.015	−2.05743	−2.02702
10°	1.026	2.15528	2.10066	190°	1.026	−2.11723	−2.06357
15°	1.059	2.02846	1.91544	195°	1.059	−2.17769	−2.05636
20°	1.097	1.89617	1.72850	200°	1.097	−2.23886	−2.04089
25°	1.131	1.75792	1.55430	205°	1.131	−2.30020	−2.03377
30°	1.196	1.61379	1.34932	210°	1.196	−2.36045	−1.97362
35°	1.250	1.46436	1.17148	215°	1.250	−2.41758	−1.93406
40°	1.312	1.31059	0.99892	220°	1.312	−2.46862	−1.88157
45°	1.389	1.15367	0.83057	225°	1.389	−2.50953	−1.80671
50°	1.445	0.99488	0.68849	230°	1.445	−2.53492	−1.75426
55°	1.489	0.83542	0.56106	235°	1.489	−2.53788	−1.70441
60°	1.581	0.67640	0.42783	240°	1.581	−2.50966	−1.58738
65°	1.619	0.51875	0.32041	245°	1.619	−2.43955	−1.50682
70°	1.664	0.36322	0.21828	250°	1.664	−2.31500	−1.39122
75°	1.711	0.21041	0.12297	255°	1.711	−2.12228	−1.24037
80°	1.725	0.06076	0.03522	260°	1.725	−1.84806	−1.07133
85°	1.744	−0.08541	−0.04897	265°	1.744	−1.48217	−0.84986
90°	1.744	−0.22787	−0.13065	270°	1.744	−1.02104	−0.58545
95°	1.744	−0.36657	−0.21018	275°	1.744	−0.47413	−0.27186
100°	1.725	−0.50110	−0.29049	280°	1.725	0.13586	0.07875
105°	1.711	−0.63145	−0.36905	285°	1.711	0.77176	0.45105
110°	1.664	−0.75750	−0.45522	290°	1.664	1.38783	0.83403
115°	1.619	−0.87910	−0.54298	295°	1.619	1.93947	1.19794
120°	1.581	−0.99604	−0.63000	300°	1.581	2.39304	1.51362
125°	1.489	−1.10813	−0.74421	305°	1.489	2.73195	1.83475
130°	1.445	−1.21513	−0.84092	310°	1.445	2.95670	2.04615
135°	1.389	−1.31681	−0.94802	315°	1.389	3.08044	2.21773
140°	1.312	−1.41294	−1.07693	320°	1.312	3.12279	2.38017
145°	1.250	−1.50338	−1.20270	325°	1.250	3.10458	2.48366
150°	1.196	−1.58807	−1.32781	330°	1.196	3.04453	2.54559
155°	1.131	−1.66715	−1.47404	335°	1.131	2.95770	2.61511
160°	1.097	−1.74094	−1.58700	340°	1.097	2.85520	2.60273
165°	1.059	−1.81001	−1.70916	345°	1.059	2.74451	2.59160
170°	1.026	−1.87516	−1.82764	350°	1.026	2.68010	2.56345
175°	1.015	−1.93740	−1.90876	355°	1.015	2.51408	2.47692

*Φ is the central angle increasing counterclockwise from $\Phi = 0$ on the major hemiaxis a along the positive axis of X through $\Phi = 90°$ on the positive Z axis, along the hemiminor axis b. The dipole center is X = 3 cm., Z = −7.069 cm. The poles of the dipole are 2.5 cm. apart. Under *Resist.* are the values in megohms for weighting each of the 72 boundary electrode potentials. The resistors are accurate through 4 numbers, a tolerance of 0.1 per cent. Under *Pot.* V_s are the 72 potentials (determined by the 650 IBM computer). Here, the dipole moment A of the Nelson formula was equal to 10. The major hemiaxis is $a = 24.817$ cm. The hemiminor axis is $b = 18.8$ cm. Under *Pot.* V'_s are the weighted values of the potential obtained by V_s/Resist. for any given value of Φ. The error on the central terminal is $V_{TW} = \Sigma \frac{V'_s}{72} = -0.00007$. This value is not greater than 0.004 per cent of the average value of the boundary potentials computed.

Tables I and II give the potentials V_s on the 72 boundary electrodes. They are theoretical values determined by the C. V. Nelson formula,[4] which was programmed on the 650 IBM computer.[5] In Table I the axis of the dipole is parallel to the positive axis of X. In Table II the axis of the dipole is parallel to the positive axis of Z. These theoretical values are to be compared with the experimentally measured values on the model (Fig. 1), where corresponding dipole positions were used (see Tables III and IV). The moment of the dipole for Tables I and II was 10 times the value $A = \rho I/2\pi d = 1$ of the Nelson formula.[4]

Reference to the legends under Tables I and II discloses that the reference potential V_{TW} of the weighted central terminal ($= \Sigma \frac{V'_s}{72} = 0.00006$) is not greater than 0.004 per cent of the average value of the potential measured. For the experimental counterpart in Tables III and

TABLE II. BOUNDARY POTENTIALS USING THE NELSON FORMULA AND THE FRANK ELLIPSE WITH DIPOLE 13*

Φ	POT. V_s	POT. V'_s	Φ	POT. V_s	POT. V'_s
0°	0.68531	0.68531	180°	0.44169	0.44169
5°	0.80837	0.79642	185°	0.35832	0.35302
10°	0.92087	0.89753	190°	0.26812	0.26132
15°	1.02495	0.96784	195°	0.16854	0.15915
20°	1.12166	1.02247	200°	0.05689	0.05185
25°	1.21128	1.07098	205°	−0.06958	−0.06152
30°	1.29348	1.08150	210°	−0.21361	−0.17860
35°	1.36762	1.09409	215°	−0.37796	−0.30236
40°	1.43305	1.09226	220°	−0.56534	−0.43089
45°	1.48918	1.07212	225°	−0.77836	−0.56037
50°	1.53565	1.06273	230°	−1.01941	−0.70547
55°	1.57233	1.05596	235°	−1.29036	−0.86659
60°	1.59928	1.01156	240°	−1.59212	−1.00703
65°	1.61676	0.99861	245°	−1.92380	−1.18826
70°	1.62511	0.97662	250°	−2.28163	−1.37117
75°	1.62479	0.94961	255°	−2.65730	−1.55306
80°	1.61627	0.93696	260°	−3.03626	−1.76015
85°	1.60004	0.91745	265°	−3.39608	−1.94729
90°	1.57655	0.90398	270°	−3.70657	−2.12532
95°	1.54624	0.88660	275°	−3.93109	−2.25406
100°	1.50960	0.87513	280°	−4.03515	−2.33921
105°	1.46702	0.85740	285°	−3.99466	−2.33469
110°	1.41892	0.85271	290°	−3.80513	−2.28673
115°	1.36571	0.84355	295°	−3.48478	−2.15242
120°	1.30785	0.82722	300°	−3.06932	−1.94137
125°	1.24582	0.83668	305°	−2.60159	−1.74720
130°	1.18017	0.81672	310°	−2.12122	−1.46797
135°	1.11150	0.80021	315°	−1.65843	−1.19397
140°	1.04045	0.79302	320°	−1.23236	−0.93929
145°	0.96773	0.77418	325°	−0.85248	−0.68198
150°	0.89399	0.74698	330°	−0.52116	−0.43575
155°	0.81978	0.72482	335°	−0.23619	−0.20883
160°	0.74549	0.67957	340°	0.00721	0.00657
165°	0.67115	0.63375	345°	0.21500	0.20302
170°	0.59639	0.58127	350°	0.39343	0.38346
175°	0.52033	0.51264	355°	0.54844	0.54033

*Dipole eccentricity is similar to that for Table I, except that the axis of the eccentric dipole is now collinear with the positive axis of Z. The dipole midpoint is at X = 3 cm., Z = −0.7069 cm. The average value of the weighted potentials under *Pot.* V'_s is $V_{TW} = \Sigma \frac{V'_s}{72} = 0.00006$, which represents the error on the central terminal. This value is not greater than 0.004 per cent of the average value of the boundary potentials computed. The resistor values are the same for all tables.

IV the potential V_{TW} of the weighted central terminal ($= \Sigma \frac{V'_s}{72} = 0.004$) is not greater than 0.24 per cent of the average value of the potential measured.

It is interesting that the potentials V_s of Tables I and II, III and IV, and V and VI may be used to plot a voltage map or "image space," and in each of the three sets the voltage map shows that the potentials fall on the circumference of a circle. For example, let us choose Tables I and II and with the equation for the circle in the form:

TABLE III. BOUNDARY POTENTIALS MEASURED ON THE MODEL ELLIPSE (FIG. 1) FOR DIPOLE POSITION 13*

Φ	POT. V_s	POT. V'_s	Φ	POT. V_s	POT. V'_s
0°	2.430	2.430	180°	−2.090	−2.090
5°	2.350	2.315	185°	−2.120	−2.089
10°	2.220	2.164	190°	−2.200	−2.144
15°	2.100	1.983	195°	−2.220	−2.096
20°	2.000	1.823	200°	−2.300	−2.097
25°	1.900	1.680	205°	−2.370	−2.095
30°	1.760	1.471	210°	−2.420	−2.023
35°	1.600	1.280	215°	−2.480	−1.984
40°	1.420	1.082	220°	−2.520	−1.921
45°	1.300	0.936	225°	−2.600	−1.872
50°	1.120	0.775	230°	−2.600	−1.799
55°	0.880	0.591	235°	−2.600	−1.746
60°	0.800	0.506	240°	−2.540	−1.606
65°	0.600	0.371	245°	−2.500	−1.544
70°	0.415	0.249	250°	−2.380	−1.430
75°	0.225	0.131	255°	−2.200	−1.286
80°	0.100	0.058	260°	−1.950	−1.130
85°	−0.150	−0.086	265°	−1.600	−0.917
90°	−0.175	−0.100	270°	−1.100	−0.631
95°	−0.250	−0.143	275°	−0.600	−0.344
100°	−0.300	−0.174	280°	0.110	0.064
105°	−0.750	−0.438	285°	0.750	0.438
110°	−0.900	−0.541	290°	1.400	0.841
115°	−1.000	−0.618	295°	2.000	1.235
120°	−1.080	−0.683	300°	2.470	1.562
125°	−1.200	−0.806	305°	2.820	1.894
130°	−1.350	−0.934	310°	3.050	2.111
135°	−1.430	−1.029	315°	3.170	2.282
140°	−1.450	−1.105	320°	3.220	2.454
145°	−1.600	−1.280	325°	3.200	2.560
150°	−1.700	−1.421	330°	3.200	2.675
155°	−1.780	−1.574	335°	3.090	2.732
160°	−1.820	−1.659	340°	2.950	2.689
165°	−1.920	−1.813	345°	2.820	2.663
170°	−2.000	−1.949	350°	2.700	2.631
175°	−2.020	−1.990	355°	2.600	2.561

*The unipolar boundary potentials V_s are measured with respect to the potential of the weighted central terminal. The weighted potentials appear under *Pot.* V'_s. The potential of the central terminal is given by $V_{TW} = \Sigma \frac{V'_s}{72} = 0.004$ for the model shown in Fig. 1. These experimentally determined values are to be compared with the theoretically predicted values offered in Table I, wherein dipole location and axis direction are similar. All values presented here are in centimeters, peak-to-peak read from the oscilloscope. They can be converted to millivolts by multiplying by 20. They are not to be compared quantitatively with those in Table I, for it was difficult to adjust the dipole generator (dipole moment) to an exact value comparable to that for Table I, for which the electrode at Φ = 0° commenced the set of measurements of unipolar potentials. The results are excellent, however, for the potential is noted to become maximal or minimal at the correct electrode. Also, the potential reverses sign between the correct pairs of boundary electrodes.

$$(X_1 - h)^2 + (Z_1 - K)^2 = R^2$$
$$(X_2 - h)^2 + (Z_2 - K)^2 = R^2$$
$$(X_3 - h)^2 + (Z_3 - K)^2 = R^2$$

For values of X_1, X_2, and X_3, we may choose the potentials from Table I, say, where the electrodes are at $\Phi = 0°$, $\Phi = 260°$, $\Phi = 300°$, respectively. Then from Table II, we must choose the potentials for the electrodes positioned at $\Phi = 0°$, $\Phi = 260°$, $\Phi = 300°$ for the corresponding values of Z_1, Z_2, and Z_3, respectively. We insert these values in the equation and solve for h and K, the coordinates of the center of the circle, and for R, the radius of the circle. The result is h = 0.286814, K = −1.189295, and R = 2.322879.

The model in Fig. 1, or the mathematical model of Tables I, II, V, VI were chosen as a close approximation for the torso-ellipse at the heart level. Since the "image space" for the dipole potentials in the ellipse is a circle, it is *not* "surprising" that the "image space" for thorax potentials on the torso-model at the heart level should have a circular configuration. If the potential function

TABLE IV. BOUNDARY POTENTIALS MEASURED ON THE MODEL ELLIPSE (FIG. 1) FOR DIPOLE POSITION 13*

Φ	POT. V_s	POT. V'_s	Φ	POT. V_s	POT. V'_s
0°	0.800	0.800	180°	0.550	0.550
5°	0.850	0.837	185°	0.480	0.473
10°	1.010	0.984	190°	0.320	0.312
15°	1.130	1.067	195°	0.220	0.208
20°	1.230	1.121	200°	0.100	0.091
25°	1.330	1.176	205°	−0.100	−0.088
30°	1.420	1.187	210°	−0.250	−0.209
35°	1.500	1.200	215°	−0.500	−0.400
40°	1.530	1.166	220°	−0.680	−0.518
45°	1.600	1.152	225°	−0.900	−0.648
50°	1.670	1.156	230°	−1.100	−0.761
55°	1.700	1.142	235°	−1.350	−0.907
60°	1.750	1.107	240°	−1.680	−1.063
65°	1.750	1.081	245°	−2.000	−1.235
70°	1.790	1.076	250°	−2.350	−1.412
75°	1.790	1.046	255°	−2.670	−1.560
80°	1.790	1.038	260°	−3.070	−1.780
85°	1.790	1.026	265°	−3.470	−1.990
90°	1.730	0.992	270°	−3.800	−1.989
95°	1.700	0.975	275°	−4.000	−2.293
100°	1.680	0.974	280°	−4.100	−2.377
105°	1.600	0.935	285°	−4.070	−2.379
110°	1.560	0.937	290°	−3.970	−2.386
115°	1.500	0.926	295°	−3.600	−2.223
120°	1.470	0.930	300°	−3.250	−2.056
125°	1.400	0.940	305°	−2.800	−1.880
130°	1.300	0.900	310°	−2.300	−1.592
135°	1.220	0.878	315°	−1.930	−1.389
140°	1.170	0.892	320°	−1.500	−1.143
145°	1.140	0.912	325°	−1.200	−0.960
150°	1.000	0.836	330°	−0.700	−0.585
155°	0.950	0.840	335°	−0.400	−0.354
160°	0.900	0.820	340°	−0.100	−0.091
165°	0.790	0.746	345°	0.220	0.208
170°	0.720	0.702	350°	0.480	0.468
175°	0.640	0.630	355°	0.640	0.630

***The unipolar potentials under *Pot.* V_s are measured with respect to the potential of the weighted central terminal V_{TW} = 0.004. The dipole location is similar to that for Table III; the dipole axis is now directed parallel to the positive Z axis. The measured unipolar potentials under *Pot.* V_s are to be compared proportionally with the theoretically predicted values under *Pot.* V_s of Table II.**

for the eccentric dipole in the sphere[6] is used to compute the surface potentials on the great circle, the plane of which contains the eccentricity and the dipole axis, the voltage map or "image space" from two arbitrary dipole directions is also given by a *circle*. However, there is one very important difference in the voltage map for the sphere when compared to that for the ellipse. The average value for the ellipse does not approach zero; hence there is need for *weighting* the central terminal. For example, if the central terminal in Fig. 1 had been unweighted by using *equal* resistors, the error for the reference potential V_{TW} of the central terminal would have been increased by more than two thousand times.

The measurements on dipole eccentricity that are shown in Table VII are very critical, and, at the same time, they are very easy to make experimentally. The dipole midpoint remains

TABLE V. BOUNDARY POTENTIALS USING THE NELSON FORMULA AND THE FRANK ELLIPSE WITH DIPOLE 55*

Φ	POT. V_s	POT. V'_s	Φ	POT. V_s	POT. V'_s
0°	2.70732	2.70732	180°	−1.66449	−1.66449
5°	2.43130	2.39536	185°	−1.62423	−1.60022
10°	2.17265	2.11759	190°	−1.74817	−1.70386
15°	1.92735	1.81998	195°	−1.79317	−1.69326
20°	1.69290	1.54602	200°	−1.84111	−1.67831
25°	1.46808	1.29803	205°	−1.89243	−1.67323
30°	1.25267	1.04738	210°	−1.94740	−1.62826
35°	1.04700	0.83760	215°	−2.00613	−1.60490
40°	0.85157	0.64906	220°	−2.06858	−1.57906
45°	0.66680	0.48005	225°	−2.13453	−1.53673
50°	0.49289	0.34110	230°	−2.20363	−1.52500
55°	0.32980	0.22149	235°	−2.27523	−1.52802
60°	0.17722	0.11209	240°	−2.34834	−1.48535
65°	0.03467	0.02141	245°	−2.42139	−1.49560
70°	−0.09845	−0.05916	250°	−2.49189	−1.49753
75°	−0.22282	−0.13022	255°	−2.55588	−1.49379
80°	−0.33912	−0.19659	260°	−2.60706	−1.51133
85°	−0.44805	−0.25690	265°	−2.63536	−1.51110
90°	−0.55026	−0.31551	270°	−2.62475	−1.50501
95°	−0.64632	−0.37059	275°	−2.54991	−1.46210
100°	−0.73680	−0.42713	280°	−2.37183	−1.37497
105°	−0.82214	−0.48050	285°	−2.03362	−1.18855
110°	−0.90276	−0.54252	290°	−1.46115	−0.87809
115°	−0.97899	−0.60468	295°	−0.58053	−0.35857
120°	−1.05110	−0.66483	300°	0.63137	0.39934
125°	−1.11930	−0.75171	305°	2.06825	1.38901
130°	−1.18377	−0.81921	310°	3.46080	2.39501
135°	−1.24464	−0.89606	315°	4.49205	3.23401
140°	−1.30202	−0.99239	320°	5.00304	3.81329
145°	−1.35603	−1.08482	325°	5.05878	4.04702
150°	−1.40682	−1.17627	330°	4.83041	4.03880
155°	−1.45461	−1.28612	335°	4.47099	3.88443
160°	−1.49973	−1.36711	340°	4.07527	3.71492
165°	−1.54262	−1.45667	345°	3.68976	3.48419
170°	−1.58388	−1.54374	350°	3.33225	3.24780
175°	−1.62423	−1.60022	355°	3.00586	2.96143

*Here and in Table VI the dipole midpoint is positioned at X = 9.25 cm., Z = −9.25 cm., in the elliptical conductor a/b = 1.32. The poles are 2.5 cm. apart. The direction of the dipole axis is parallel to the positive axis of X. The potentials V_s are computed by the 650 IBM computer through 8 significant digits. These potentials have been reduced through 6 significant digits. The dipole moment A of the Nelson formula has been arbitrarily taken as 10. The computed value for the potential of the weighted central terminal is $V_{TW} = \bar{V}'_s = \Sigma \frac{V'_s}{72} = 0.00004$. These dipole positions correspond *approximately* with Frank's dipole position 55.

on the ± axis of X, and the direction of the dipole axis is parallel to the positive axis of X or along the major axis of the ellipse. For any particular boundary electrode indicated by the central angle Φ the dipole is moved along the X axis until the detector shows a null; that is, when $(V_s - V_{TW}) = 0$. The eccentric position of the dipole is then measured with a centimeter ruler calibrated in 0.05 cm. The measured values can then be compared with the computed values (Table VII).

DISCUSSION

The generator and detector circuits used with these experiments are essentially similar to those described in studying the circular homogeneous lamina.[2]

If the conductor extends throughout the region contained by a closed surface S (or throughout a two-dimensional region contained by a closed-plane curve), and, moreover, extends without limit beyond the boundary surface of the region

TABLE VI. BOUNDARY POTENTIALS USING THE NELSON FORMULA AND THE FRANK ELLIPSE WITH DIPOLE 55*

Φ	POT. V_s	POT. V'_s	Φ	POT. V_s	POT. V'_s
0°	1.42682	1.42682	180°	0.38709	0.38709
5°	1.52896	1.50636	185°	0.34317	0.33809
10°	1.60386	1.56321	190°	0.29627	0.28876
15°	1.65734	1.56500	195°	0.24510	0.23144
20°	1.69309	1.54338	200°	0.18828	0.17163
25°	1.71361	1.51512	205°	0.12444	0.11002
30°	1.72078	1.43877	210°	0.05218	0.04362
35°	1.71623	1.37298	215°	−0.02994	−0.02395
40°	1.70152	1.29689	220°	−0.12351	−0.09413
45°	1.67816	1.20817	225°	−0.23033	−0.16582
50°	1.64762	1.14022	230°	−0.35256	−0.24398
55°	1.61124	1.08209	235°	−0.49281	−0.33096
60°	1.57021	0.99317	240°	−0.65437	−0.41389
65°	1.52556	0.94228	245°	−0.84138	−0.51969
70°	1.47815	0.88831	250°	−1.05905	−0.63644
75°	1.42867	0.83499	255°	−1.31402	−0.76798
80°	1.37766	0.79864	260°	−1.61456	−0.93597
85°	1.32557	0.76007	265°	−1.97086	−1.13008
90°	1.27271	0.72976	270°	−2.39523	−1.37341
95°	1.21928	0.69912	275°	−2.89915	−1.66235
100°	1.16560	0.67571	280°	−3.49198	−2.02433
105°	1.11178	0.64978	285°	−4.16978	−2.43704
110°	1.05795	0.63578	290°	−4.89555	−2.94203
115°	1.00427	0.62030	295°	−5.56582	−3.43781
120°	0.95088	0.60144	300°	−5.98316	−3.78441
125°	0.89793	0.60304	305°	−5.90277	−3.96425
130°	0.84562	0.58520	310°	−5.20865	−3.60460
135°	0.79414	0.57173	315°	−4.06109	−2.92375
140°	0.74373	0.56685	320°	−2.78335	−2.12145
145°	0.69459	0.55567	325°	−1.63185	−1.30548
150°	0.64692	0.54090	330°	−0.71149	−0.59489
155°	0.60083	0.53123	335°	−0.02186	−0.01932
160°	0.55633	0.50713	340°	0.47929	0.43690
165°	0.51323	0.48463	345°	0.83979	0.79300
170°	0.47113	0.45919	350°	1.09959	1.07172
175°	0.42939	0.42304	355°	1.28835	1.26931

*The dipole midpoint position is the same as that described in the footnote of Table V. The direction of the dipole axis is now parallel to the positive Z axis. Here, $V_{TW} = \bar{V}'_s = \Sigma \frac{V'_s}{72} = 0.00000$.

specified (or beyond the boundary line of the closed-plane curve), and if the bounded region contains an electrical multipole in which the net pole strength is zero, formulation of the potential V_i is now possible at any point inside of the region where the resistivity is K_i. Also, formulation of the potential V_o at any point outside of the region is also possible where the resistivity is K_o. In these solutions of the potential we must satisfy the Laplace equation $\nabla^2 V_o = 0$ and $\nabla^2 V_i = 0$ at all points exterior to the region of the multipole. On the boundaries of the region we must have

$$\frac{\delta V_i}{\delta n} = \frac{K_i \, \delta V_o}{K_o \, \delta n}, \quad V_i = V_o \tag{2}$$

where $\delta/\delta n$ indicates differentiation along the normal to the boundary.

TABLE VII. EXPERIMENTAL AND THEORETICAL VALUES OF THE DIPOLE ECCENTRICITY ALONG ± X AXIS WHICH GIVE A ZERO OF POTENTIAL ON BOUNDARY ELECTRODES*

Φ	COMPUTED ECCENTRICITY	MEASURED ECCENTRICITY	MEASURED ECCENTRICITY
90°	± 0.00	0.00	0.00
85°	± 2.25	1.95	− 1.70
80°	± 4.15	3.65	− 3.65
75°	± 5.95	5.15	− 5.45
70°	± 7.65	7.00	− 7.15
65°	± 9.35	8.90	− 9.00
60°	±10.15	10.70	−10.75
55°	±11.95	12.50	−12.60
50°	±13.65	14.05	−14.30
45°	±15.45	15.60	−15.85
40°	±17.05	17.20	−17.55
35°	±18.85	18.90	−19.20
30°	±20.55	20.25	−20.55

*Under the central angle Φ are the boundary electrode locations. In each instance the electrode is of potential $V_s = V_{TW} = 0$ for the particular eccentricity shown under *Measured Eccentricity*. The dipole position is on the X axis, with a direction parallel to the positive axis of X (along the major axis of the ellipse). The values under *Computed Eccentricity* are those predicted by the IBM computer using the Nelson formula. The sensitivity of the detector circuit was sufficient to allow adjustment of the dipole electrode within 0.05 cm. The difference between the measured and predicted values may be ascribed to errors in model construction (Fig. 1).

If the potential V_o is now *arbitrarily* chosen to be *zero* at *infinity* in the customary way, and if, in addition, K_o is made to increase without limit in the solution for V_i, the orientation of the locus for zero values of V_i is unique within the bounded region and corresponds to the arbitrary choice of V_o being zero at infinity.[7] Moreover, it may at once be observed that this same procedure gives

$$\lim_{K_o \to \infty} \frac{\delta V_i}{\delta n} = 0 \tag{3}$$

for equation (2). Dr. Frank N. Wilson's choice of dipole "midpoint potential" as "zero" for V_i also corresponds to zero value for V_o at infinity. Having made this customary choice of zero value for V_i, which corresponds to the zero value

for V_o at infinity, we may utilize Gauss' theorem on the mean,[8] which states that the average value $\bar{V}_s$ of the potential V_s over the surface S of a homogeneous spherical conductor due to a pole located anywhere within S is the same as if the pole were located at the center of S. If two poles are chosen of equal strength and opposite sign (dipole, source and sink), the average value is given by[9]

$$\bar{V}_s = \frac{1}{4\pi R^2} \iint_s V_s \, ds = 0 \tag{4}$$

wherein V_s is the value of V_i at any point on S, and R is the radius of the sphere.

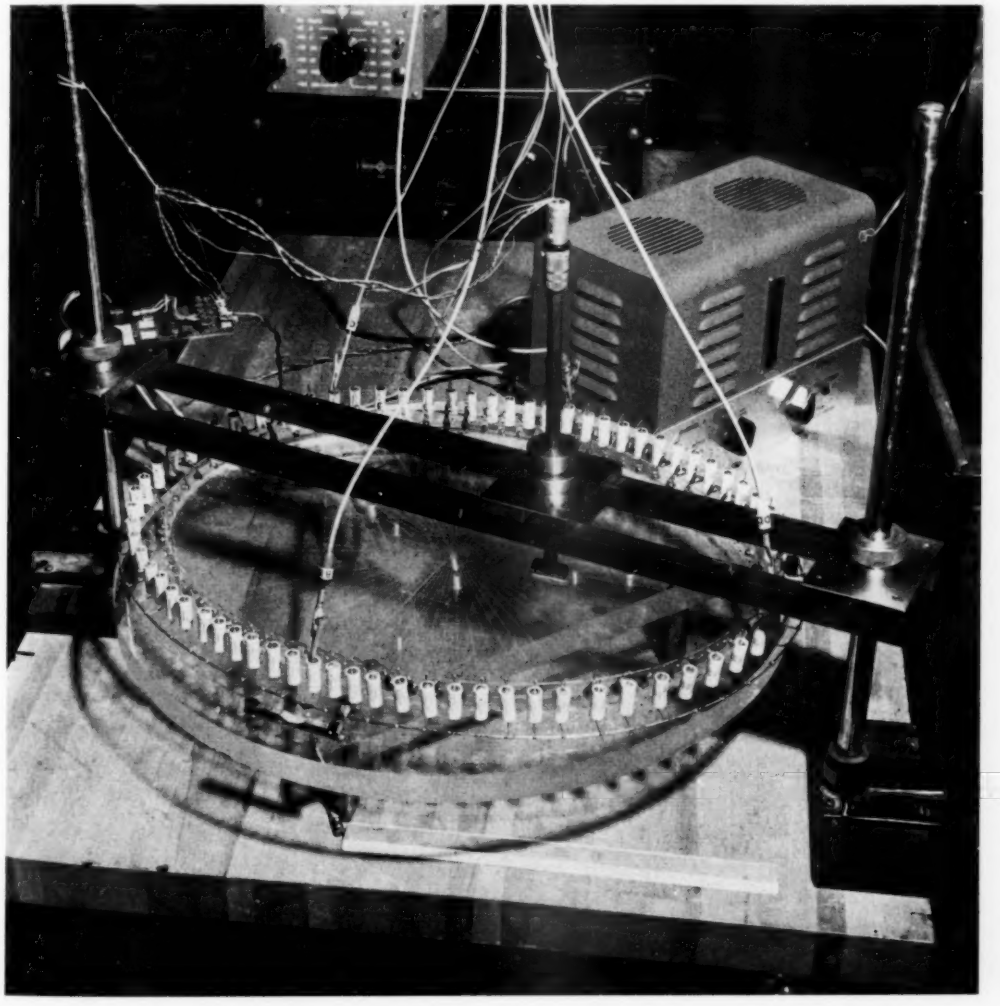

Fig. 1.—The elliptical dish, containing tap water, may be seen resting upon a tripod leveling table. Over the dish is the dipole suspension platform. The dipole proper is observed at an eccentric position along the major axis of the ellipse. The boundary electrodes are small silver-plated screws fixed through the vertical rim of the elliptical dish. Exterior to the dish the electrodes can be seen connected to the central terminal (wire-ring) through the vertically mounted resistors. The values of the resistors (Allen-Bradley) are given in Table I. Four detector probes (at the end of the white shielded cables) may be observed clipped on to four of the boundary electrodes.

Equation (4) also holds for the potential of the general multipole in which the net pole strength is zero; that is[9]

$$\bar{V}_s = \frac{1}{4\pi R^2} \sum_{1}^{n} \iint_{s} V_s \, ds = 0, \tag{5}$$

wherein n is the number of poles taken two at a time, V_s is the potential at any point of S due to any two poles located arbitrarily within S, and R is the radius of the sphere. The surface integrals of the potential in equation (5) vanish separately for the general multipole in which the first term for the solution of the potential V_s is that due to a dipole, the second term is that due to a quadripole, and the third term is that due to an octipole, and additional terms are of increasingly higher order.

We may safely assume that the electrical field generated by the heartbeat is represented by a multipole of this kind described above, and that equation (5) or its extension is the most satisfactory, if not the *only*, way of defining (for experimental purposes) the "zero" of potential within a conducting region bounded by an insulating medium. When an averaging network of potential V_{TW} (≈ 0) is desired, as in these and other experiments,[2,10-12] the objective in designing the network is to approximate as accurately as is necessary the integral given in equation (5). In this equation, S is a spherical surface, and the experimental model under study is an elliptical dish. The equation to be satisfied is[2,9]

$$\bar{V}_s = \frac{1}{2\pi R} \sum_{1}^{n} \int_{s} V_s \, ds = 0 \tag{6}$$

wherein S is a circular closed curved, n = 1 (dipole), and R is the radius of the curve. Since the ellipse is not circular, the averaging buss at the nonelectrode end of the resistors must average a group of weighted potentials V'_s which are proportional to the same potentials V_s that would occur if the lamina were *circular*. One-dimensional resistance is determined by the length of a linear conductor. Two-dimensional resistance, for which the potential varies inversely, is related to area. Three-dimensional resistance, for which the potential varies inversely, is related to volume. In the circular lamina, equal angular sectors are of equal area, and large equal resistors are used.[2] In the ellipse the equal angular sectors are not equal in area, and increasingly larger resistors are required for sectors of increasingly smaller area. The choice of the resistor for the largest sectional area is arbitrary if equal to or greater than one megohm. The large value is desirable in order not to alter the flow of current within the field. It has been determined experimentally[2] that the field is not appreciably changed by adding the averaging network to the boundary electrodes. If one is experimenting with an elliptical cylinder or an actual torso-model, a close approximation of the weighting value for the resistors does not present a difficult problem in comparison with that of solving an analytical or numerical solution of the potential due to a contained arbitrary dipole or multipole. Divide the surface into a sufficiently large number of triangles and indicate the apices by 1, 2, 3. Denote the centroid

of the volume conductor by 0. Then the value of the weighted resistor to be located at the centroid of the triangle is given by

$$\frac{1}{r} = \left[\vec{a} \times \vec{b} \cdot \vec{c}\right] \tag{7}$$

wherein $\vec{a}$ is the vector 01, $\vec{b}$ is the vector 02, and $\vec{c}$ is the vector 03.

One can always choose for a reference potential the potential of a fixed electrode on the boundary or at a point within the conductor under study. With respect to this potential, the difference in potentials between the fixed and the exploring probe can always be accurately determined with a good differential amplifier. In this way one can map out the distribution of equipotential surfaces. With a dipole or multipole which does not vary with time, the mapping problem is an easy matter. However, this is not the case with the beating heart, in which the orientation of poles rapidly changes with respect to time. Simultaneous instants of time must be determined with each new position of the exploring probe. Finally, if one then wishes to know the analytical value of the potential at a point, one must know the analytical solution of the potential at the reference (or fixed) electrode. This potential must then be subtracted from all the differences in potentials measured, in order to obtain the analytical potential at the point or points under study.[7] The analytical solution has not been determined by mathematical techniques except for homogeneous regions of simple geometrical shape, such as the two-dimensional circular lamina,[1] the two-dimensional ellipse,[4] the sphere,[6] and the oblate and the prolate spheroids.[13,14]

The Wagner ground potential utilized by Frank and Kay[15] does not conform to the above-defined "zero" reference potential, as they contend, and which is required for the measurement of unipolar leads or unipolar lead vectors. The Wagner ground potential of Frank and Kay is, in fact, a function of both dipole position and rotation.[2] The elaborate tables published by Frank[3] do not represent a sound system of unipolar lead vectors. When regarded as such, the errors vary from 10 to 150 per cent of the true unipolar potential being measured. In general, the error increases with increasing dipole eccentricity. Consequently, no proper evaluation of the error on the Wilson central terminal may be based on these studies. The Wilson central terminal is, in fact, a first-order approximation to the highly accurate zero of potential of a weighted central terminal of the kind utilized here in the two-dimensional ellipse.

It is clear, therefore, that aside from dipole position and important differences in conductivity of regions of the conductor an attempt must be made to consider the effects on the field produced by the form and character of the boundary conditions.

The importance of the averaging network, unweighted or weighted, in attempting measurements of unipolar potentials has been repeatedly emphasized.[1,2,9-12] The present studies with a weighted central terminal represent additional advances in the use of an averaging network for a central terminal of potential zero, by the use of which accurate unipolar measurements may be made on the homogeneous elliptical lamina. Using Tables I and II or V and VI, one can decrease the number of electrodes in a symmetrical fashion and observe

an increasing nonzero error on the weighted central terminal. In this way a necessary minimal number of resistors can be determined according to the acceptable error.

SUMMARY

A method is described by which accurate measurement of unipolar potentials may be made on the homogeneous elliptical lamina. Measurement of unipolar potentials are made with the reference potential V_{TW} of the weighted central terminal connected to 72 electrodes on the boundary of the ellipse. The measured unipolar potentials on the model compare in a highly satisfactory manner with the theoretically predicted values obtained by programming the C. V. Nelson formula on the 650 IBM computer.

The method of extending the weighting process to the three-dimensional conductor is briefly described. The properly devised averaging network must approximate the value of the integral in equations (5) or (6). Under certain circumstances an integrating electrode may be used.[9] The Wagner ground potential of Frank and Kay is a function of both dipole position and dipole rotation[2] and is an unsound reference for the measurement of unipolar potentials. The weighted or unweighted central terminal (averaging network) or the integrating electrode are, in the author's opinion, the only means by which unipolar potentials or unipolar lead vectors can be measured in models or approximated in man.[12] The general method is equally useful where the field is due to a multipole (of zero net pole strength).

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The Ventricular Gradient Vector and Related Vectors

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The main purpose of this article is to define the cardiac complex area vector and to discuss its significance as it relates to the ventricular gradient area vector. Studies of the variation of the ventricular gradient area vectors in several cases of intermittent conduction disturbance are presented.

BASIC CONCEPTS

The arithmetic mean or average value of n scalars is their algebraic sum divided by the number n. The scalar voltage recorded by an electrocardiograph is a function of time. An approximate mean value of the voltage with respect to time may be obtained for any particular interval of time by dividing this interval into n equal subintervals of time, constructing an ordinate from the base line to the curve at the midpoint of each subinterval and then averaging the n ordinates as shown in Fig. 1,*C*. The error of this approximation obviously tends to decrease as the number of time subintervals and corresponding ordinates are increased.

The mean value of the voltage with respect to time for a given interval of time is defined by the following,

$$[\text{Mean value of v with respect to time from } t = t_o \text{ to } t = t_1] = \frac{\int_{t_o}^{t_1} v\,dt}{t_1 - t_o} \qquad (1)$$

where the numerator on the right is the definite integral giving the area bounded by the curve of recorded voltage, v, the base line and the ordinates $t = t_o$ and $t = t_1$.

The mean or average vector of n vectors is their vector sum divided by the number n. In general, the direction of the mean vector of n vectors is not the mean of the directions of the n vectors, and the magnitude of the mean vector is not the mean of the magnitudes of the n vectors. The heart vector H may be considered an explicit function of time. An approximate mean vector with respect

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to time for a particular portion of a vectorcardiogram may be graphically obtained by dividing this portion of the loop into n equal subintervals of time, constructing a vector from the origin to the loop at the midpoint of time of each subinterval, adding the n constructed vectors vectorially and dividing the magnitude of this vector sum by n, as shown in Fig. 1,*D*.

The mean heart vector with respect to time for the time interval from t_o to t_1 is defined by the following,

$$[\text{Mean H with respect to time from } t = t_o \text{ to } t = t_1] = \frac{\int_{t_o}^{t_1} \text{Hdt}}{t_1 - t_o} \tag{2}$$

where the numerator on the right is the area heart vector for the time interval from t_o to t_1.

An area heart vector for any particular interval of time is equal to the mean heart vector with respect to time for this particular time interval multiplied by this time interval. The determination of an area vector from measurement of electrocardiographic complexes is depicted in Fig. 2.

Hecht[1] has stated that it is obvious that the area which is enclosed by a vectorcardiogram is identical with the area vector for the corresponding electrocardiographic deflection. On the contrary, it is obvious that this is not true. The area enclosed by a vectorcardiogram is related to the area vector determined from the vectorcardiogram or the corresponding electrocardiogram only in a complex fashion of no practical significance.

If it is considered that the ventricular gradient process and the repolarization process both extend throughout the QU interval, Wilson's hypothesis may be stated as follows,

$$t_{QRS}M_{QRS} + t_{QU}M_{TU} = t_{QU}M_G \tag{3}$$

where t_{QRS} and t_{QU} are the QRS and QU intervals, respectively, and M_{QRS}, M_{TU}, and M_G are the mean vectors with respect to time for QRS, TU, and the ventricular gradient, respectively.

If an isolated PT_a complex is available, the areas of the P and T_a waves can be accurately approximated. Since the initial portion of atrial repolarization occurs during atrial depolarization, it may be considered that the P wave rests upon the initial portion of the T_a wave, as shown in Fig. 3. This initial portion of the T_a wave may be approximated by drawing a straight line between the points of onset and offset of the P wave. The net area of the P wave may then be approximated by measuring with respect to this constructed straight line. The T_a wave may be considered to be based upon the true base line which may be approximated by drawing a straight line between the points of onset and offset of the T_a wave. The area of the T_a wave is obtained, therefore, by measuring with respect to this constructed straight base line.

The P and T_a waves overlap in the area enclosed by the straight line drawn to approximate the initial portion of the T_a wave, the straight base line constructed between the points of onset and offset of the T_a wave, and the portion

of the curve of the P wave between these two straight lines. Since this area is of opposite sign in the P and T_a areas, it will cancel when the P and T_a areas are added to obtain the net area of the PT_a complex. Consequently, it is unnecessary to define the initial portion of the T_a wave, the base of the P wave, to obtain the net PT_a area. The net PT_a area may be obtained simply by measuring the area

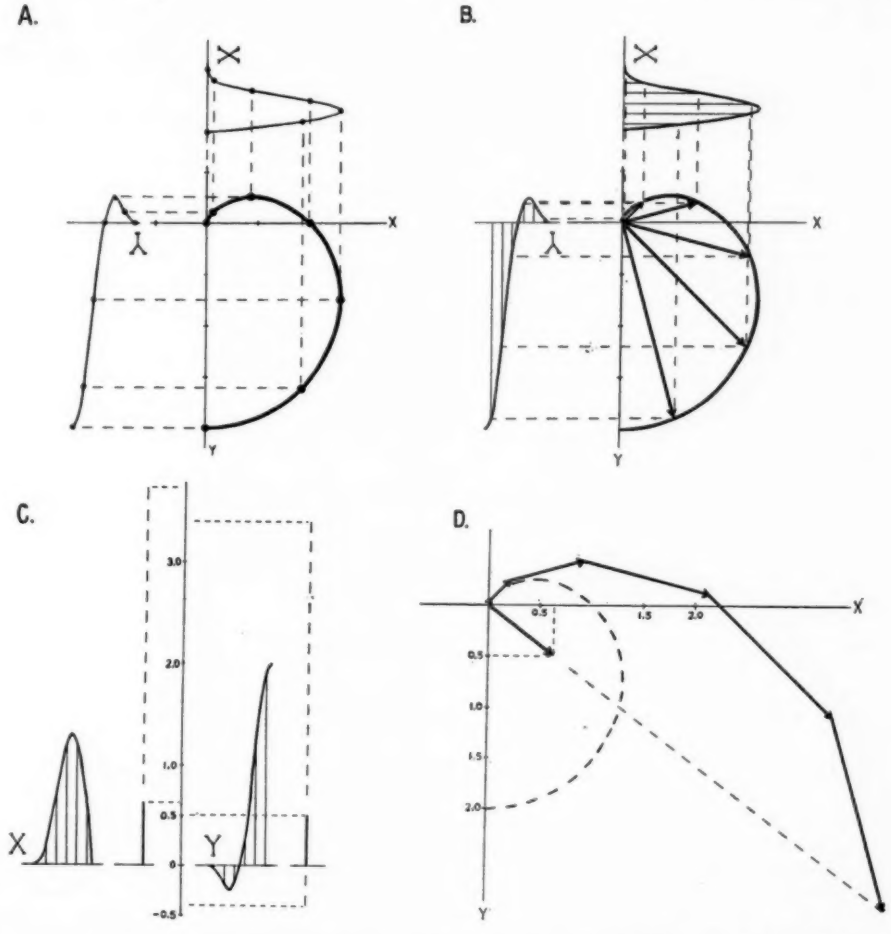

Fig. 1.—*A*, The first 0.06 sec. of a QRS loop and the corresponding portions of two QRS complexes recorded by two leads, X and Y. Any two electrocardiographic leads when fed to the orthogonal paired deflection plates of an oscilloscope will yield a vectorcardiogram having the characteristic that the electrocardiograms recorded by these leads may be precisely derived from the vectorcardiogram by using an orthogonal lead diagram, and conversely, the vectorcardiogram may be precisely derived from the two simultaneously recorded electrocardiographic leads. *B*, Vectors are constructed from the origin to the time midpoints of the six equal subintervals of time along the QRS loop, and the corresponding ordinates are constructed from the base line to the curve at the midpoints of the corresponding time subintervals for the two partial QRS complexes. *C*, The constructed ordinates are added algebraically by placing them end to end, as shown by the vertical dashed lines, and the means of these algebraic sums are found by dividing by 6, the number of ordinates added. *D*, The mean values of voltage with respect to time for the two partial QRS complexes determined in *C* are used to find the corresponding mean vector with respect to time. The vectors constructed in *B* are added vectorially by the origin-to-terminus method to yield their vector sum, indicated by the dashed line. Dividing the magnitude of this vector by the number 6 yields a mean vector with respect to time equal to that determined from the electrocardiographic complexes. This approximated mean vector with respect to time differed insignificantly from the correct mean vector calculated analytically using equations (1) and (2), which calculations were possible since the functions v = f (t) and H = F (t) were known in this particular example.

under the complex with respect to the straight base line constructed between the points of onset and offset of the T_a wave.

Similar remarks apply to the measurement of the QRS, TU, and QRSTU areas of an isolated ventricular complex. It is simpler to measure the area of QRSTU directly than to obtain this area by adding the measured areas of QRS and TU.

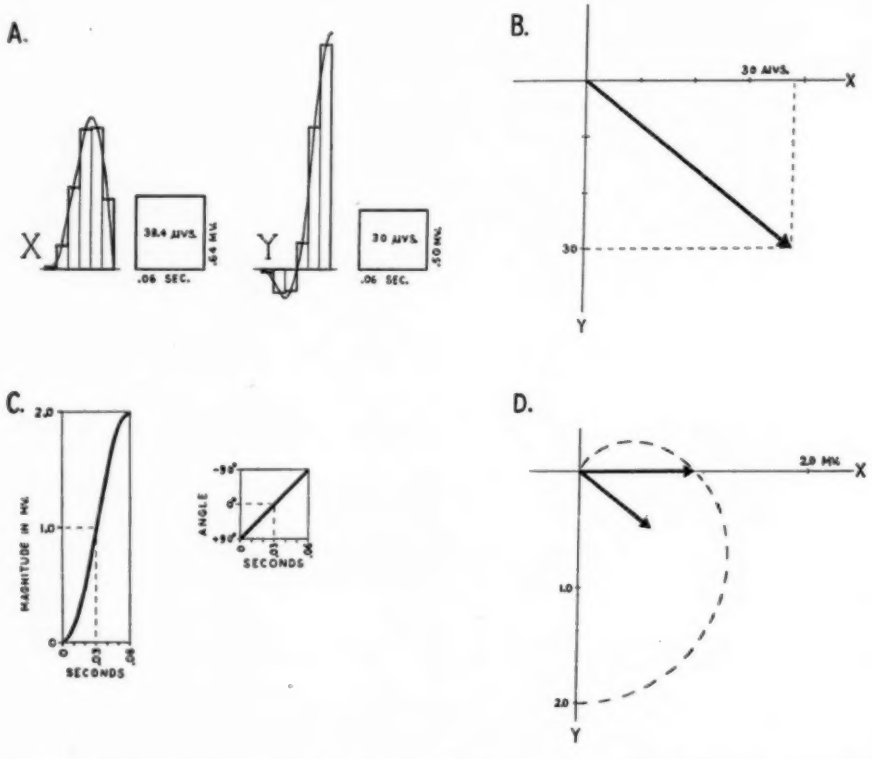

Fig. 2.—*A*, The approximate area of the first 0.06 sec. of two partial QRS complexes found by constructing rectangles with one pair of sides equal to the corresponding ordinates of Fig. 1,*B*, and the other pair equal to the time subinterval. The areas of these constructed rectangles are algebraically added to yield the sums shown by the larger rectangles. *B*, The approximate area vector determined from the values found in *A*. The same approximate area vector is obtained when the mean vector with respect to time from Fig. 1,*D* is multiplied by 0.06 sec. *C*, The variation of the magnitude and direction of the heart vector with respect to time for the partial QRS loop shown in Fig. 1. The mean magnitude and the mean direction with respect to time for these functions are indicated. *D*, The partial QRS loop is indicated by a dashed curve. The vector with magnitude and direction equal to the means indicated in *C* is shown, as is the mean vector with respect to time previously determined in Fig. 1,*D*. It is apparent, as is generally true, that the direction of the mean vector with respect to time is not the mean of the directions of the QRS vectors, and that the magnitude of the mean vector with respect to time is not the mean of the magnitudes of the QRS vectors.

In the usual cardiac complex the ventricular complex is superimposed upon the T_a wave, so that measurement of the T or TU area is further complicated by the necessity of defining the terminal portion of the T_a wave. The area of PT_aTU, however, may be simply measured with respect to a straight base line constructed between the point of onset of P and the point of offset of U, as shown in Fig. 3. The area of PT_aQRSTU is likewise measured with respect to this constructed straight base line.

In this study, the U wave is considered to be part of ventricular repolarization in regard to the ventricular gradient. If this assumption is correct and if there is no atrial gradient, the area vector found from measurement of PT_aQRSTU areas is the ventricular gradient area vector. For the studies presented in the subsequent portion of this article it is immaterial whether or not there is an atrial gradient, inasmuch as the studies are concerned with intraindividual comparisons of the PT_aQRSTU area vector over brief periods of time during which it may be assumed that the atrial gradient is constant.

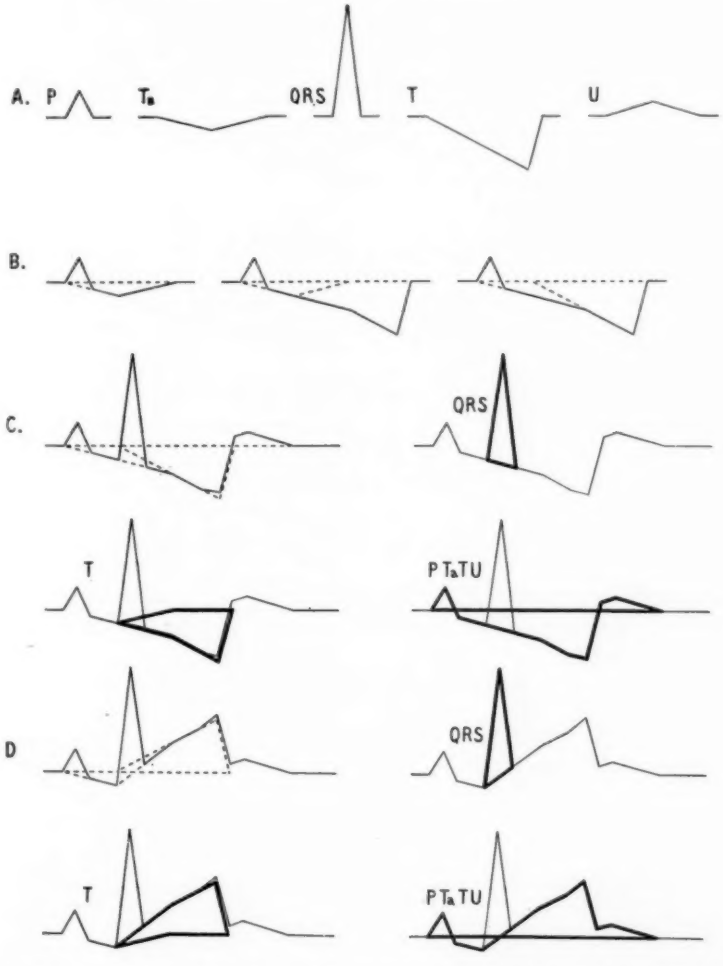

Fig. 3.—*A*, Arbitrary P, T_a, QRS, T, and U waves shown for simplicity as isosceles triangles. *B*, When the PT_a complex is formed, the shape of the P wave is altered but its area remains the same. The initial portion of the T_a wave, shown by a dashed line, now forms the base of the P wave, and each ordinate from this base line to the curve has the same length as the corresponding ordinate from the horizontal base line to the curve of the isolated P wave in *A*. Since the sign of the terminal portion of the T_a wave and the initial portion of the T wave is the same, either may be considered to originate along the horizontal base line, whereas the other is superposed. *C*, The cardiac complex is completed by adding the QRS and U waves. The heavy outlines of QRS, T, and PT_aTU indicate the course along which a planimeter should travel in measuring these areas. For measurement of the PT_aQRSTU complex the planimeter should travel along the curve of the cardiac complex and then back to the point of onset along a constructed base line extending between the points of onset and offset of the complex. *D*, A different cardiac complex is obtained by changing the sign of the T wave so that the T area is now positive. The determination of the areas of QRS, T, and PT_aTU is again shown.

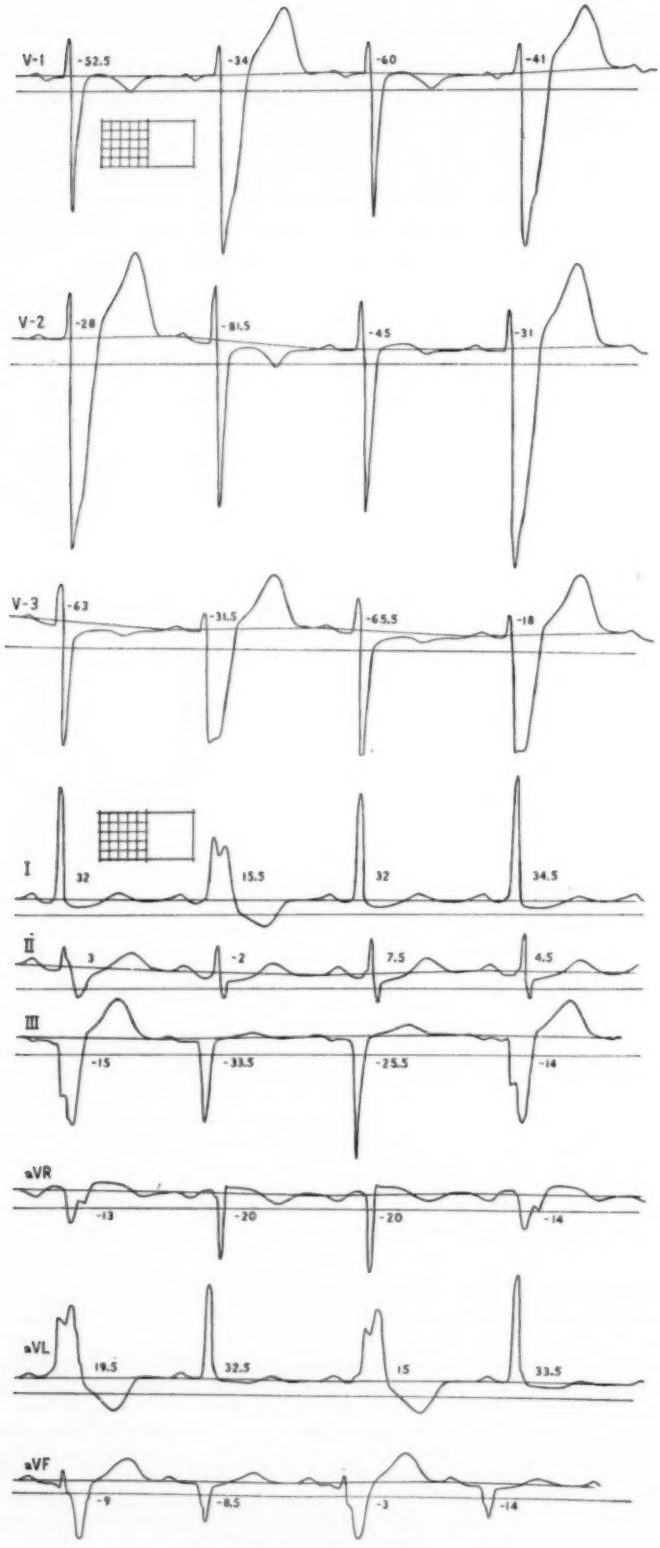

Fig. 4.—*(For legend see opposite page.)*

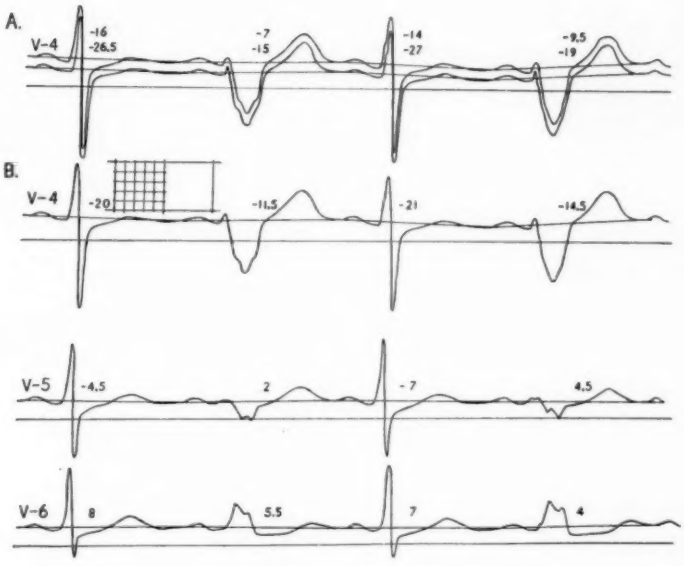

Fig. 4.—The electrocardiogram for a case of intermittent left bundle branch block. The areas of the cardiac complexes, in microvolt-sec., are written by each complex and were determined with respect to a straight line constructed between the points of onset of successive P waves. A straight line beneath each lead was constructed parallel with the original horizontal paper markings. *A*, A tracing of Lead V_4 showing the upper and lower margins of the inscribed electrocardiogram. As was true for the other leads, the areas of the cardiac complexes for the upper curve are consistently greater than those for the lower curve. *B*, A midpoint tracing of Lead V_4 constructed along the midpoints of the vertical distances between the upper and lower margin curves. Such midpoint curves are illustrated for all of the other leads.

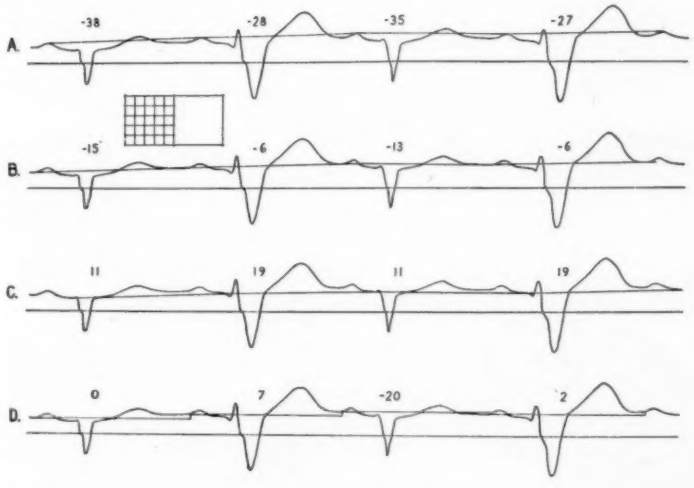

Fig. 5.—*A*, *B*, and *C*, Four complexes from Lead aVF from a case of intermittent left bundle branch block. The cardiac complex areas are measured with respect to a straight line constructed between the peaks of successive P waves, between the points of onset of successive P waves, and between the points of onset of successive QRS complexes. In each case the difference between the measured areas of the normal and abnormal complexes is approximately the same. *D*, The cardiac complex areas are measured with respect to a horizontal straight line passing through the point of onset of the P wave. Such results are the best that can be obtained with electronic integrators currently in use. Obviously, the averaging of a large number of complexes would be necessary to obtain measurements of notable accuracy.

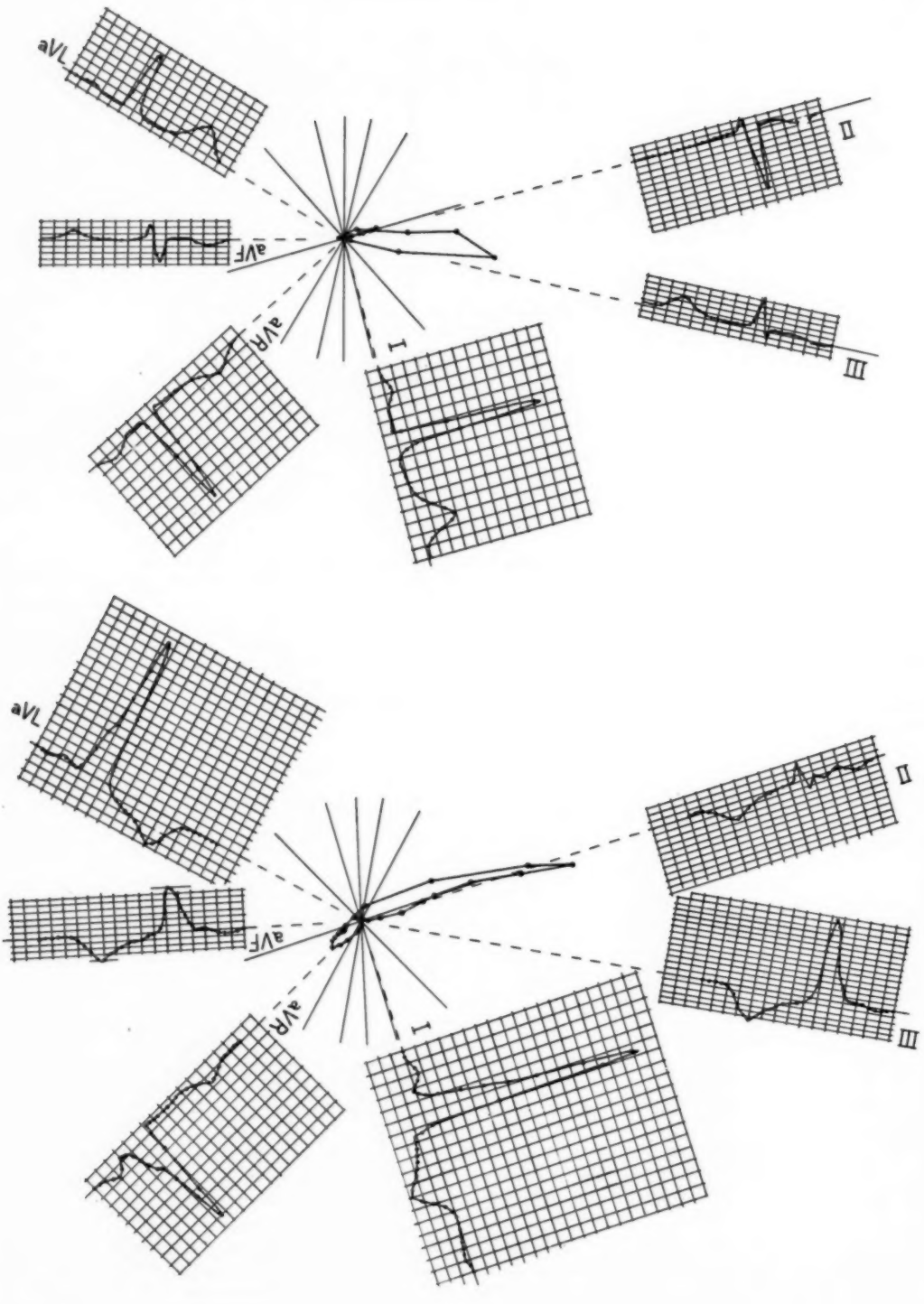

Fig. 6.—Limb lead plane vectorcardiograms derived for the normally and anomalously conducted complexes from a case of intermittent Wolff-Parkinson-White syndrome.

For the measurement of PT_aQRSTU areas undertaken in this study the original electrocardiogram or published figure was enlarged eight diameters optically, and the upper and lower margins of the inscribed electrocardiogram were traced onto paper for planimetric area determination. It was frequently

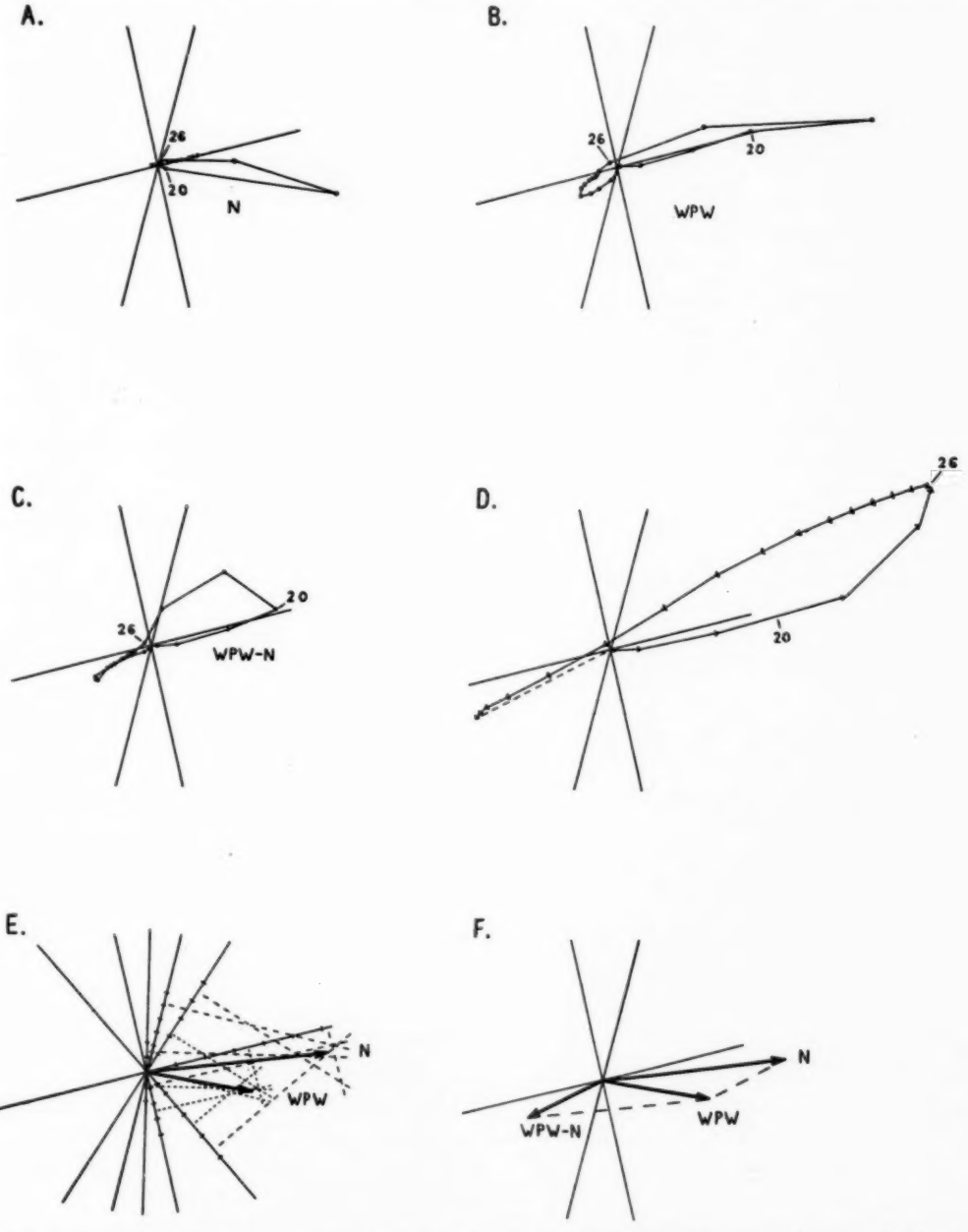

Fig. 7.—*A* and *B*, The vectorcardiograms from Fig. 6. *C*, The difference vectorcardiogram obtained by subtracting the loop in *A* from the loop in *B*. *D*, Derivation of the area vector for the difference loop in *C*. The dashed line indicates the vector sum which is to be divided by the number of vectors which were added and then multiplied by the total time interval. *E*, The card ac complex area vectors for the normally and anomalously conducted complexes obtained from the measured areas of the electrocardiographic complexes. *F*, The ventr cular gradient area difference vector obtained by subtracting the normal from the abnormal cardiac complex area vector. This vector is the same as that obtained in *D*.

found that the areas determined from the upper and lower margin curves differed. For over a hundred complexes from the case of intermittent left bundle branch block to be presented the areas were consistently algebraically greater for the upper curve. This is obviously due to the vagaries of the heated stylus, and indicates the error of the common practice of randomly changing from the upper to the lower margin in area measurement.

THE EXPERIMENT OF WILSON AND ASSOCIATES

In their original articles on the ventricular gradient, Wilson and associates[2,3] described a dog experiment performed to investigate the constancy of the ventricular gradient area vector during marked alteration of ventricular depolarization. It was decided to determine the cardiac complex area vectors for this experiment.

The values for the PT_aQRSTU areas were first determined with respect to a straight base line drawn between the points of onset of successive P waves. The measured values for Lead I decreased somewhat irregularly from approximately 15 microvolt-sec. for the first complex to zero for the fifteenth complex, with one notable exception, complex 11. The values for Lead III were close to 38 microvolt-sec., with six exceptions, complexes 1, 3, 5, 12, 13, 15. Visual examination of these complexes indicates that the base line is not accurately approximated by a straight line drawn between the points of onset of successive P waves.

Several methods were used in an attempt to find the true location of the base line, but only one such method will be described, since it reveals the general approach. The complex in question and the two preceding and two succeeding complexes were adjusted so as to bring the constructed straight base lines to a horizontal position. All five adjusted complexes were then traced onto a single piece of paper so that the points of onset of the P waves and the adjusted straight base lines were superimposed. A gradual transition of waveform from complex to complex was then apparent for all complexes save that with the erroneous base line. On the basis of such study, the seven erroneous base lines were redrawn and new values for the areas of the cardiac complexes were determined. These new values were consistent with the values previously determined for the other complexes.

The magnitude of the Lead III vector for a dog may be three times that of the Lead I vector, and the angle between these lead vectors may be close to 90°. On such a lead vector diagram the cardiac complex area vectors will vary through a range of about 50°, as the cardiac complex area in Lead I varies from about 15 to zero microvolt-sec. Thus the termini of the ventricular gradient area vectors move from left to right as the center of stimulation of the ventricles moves from right to left.

Variation of the equivalent cardiac generator with variation in the lead fields would explain the changing ventricular gradient area vectors. An alternate explanation is that Wilson's hypothesis does not hold. Apparently, the issue cannot be settled without further animal experimentation wherein the animal heart is suspended in an extensive medium with distant electrodes, thereby

ensuring relatively constant lead vectors. If the ventricular gradient area vector is constant despite alteration in depolarization in such an experiment, Wilson's hypothesis will finally have been demonstrated to hold for the isolated animal heart.

THE CASE OF SIMONSON, SCHMITT, DAHL, FRY AND BAKKEN

Simonson and associates[4] published three electrocardiograms taken over a 7-day period from a patient with right bundle branch block who subsequently developed complete atrioventricular block with a changing ventricular pacemaker. They stated that this case constitutes the human counterpart of the dog experiment of Wilson and associates. The magnitudes of the three ventricular gradient area vectors calculated from their data were similar. However, visual inspection of the Lead I complex for April 24, reveals that it has a net negative area, whereas Simonson and associates have measured the area of this complex as a net positive quantity to four significant figures. The nature of their error appears to be the use of a base line constructed along the lower margin of the inscribed curve, whereas the T area is measured along the upper margin. It appears that the authors used the second complex in Lead III on April 17, to determine the QRS area but used the first complex to determine the T area. Such a division between two QRST complexes is an illegitimate error, since, if the ventricular gradient is unchanged, the larger, second QRS would surely be followed by a larger negative T.

The cardiac complex area vectors were determined for these electrocardiograms and showed considerable variation in magnitude and direction. It is evident that the conclusions of Simonson and associates with respect to the ventricular gradient for these electrocardiograms are, in general, invalid.

INTERMITTENT RIGHT BUNDLE BRANCH BLOCK

The cardiac complex areas were determined for the case of intermittent right bundle branch block published by Wilson and associates[5] and for the case published by White.[6] In both cases the areas for the blocked complexes were roughly half the areas for the normal complexes in the right precordial leads. Since both types of complexes had positive areas in the right precordial leads, the ventricular gradient area difference vector obtained by subtracting the normal from the blocked cardiac complex area vector was directed posteriorly in both cases.

INTERMITTENT LEFT BUNDLE BRANCH BLOCK

The cardiac complex area vectors were determined for a case of intermittent left bundle branch block published by Segers and Boyadjian,[7] and the magnitude of the vector for the blocked complexes was about two thirds of the magnitude of that for the normal complexes. The ventricular gradient area difference vector obtained by subtracting the normal from the blocked cardiac complex area vector was directed rightward and slightly inferiorly.

The electrocardiogram from a previously unpublished case of intermittent left bundle branch block is shown in Fig. 4. It might be wondered whether the differences between the area measurements of the normal and blocked complexes are due to incorrect placement of the constructed base line with respect to which the measurements were made. In Fig. 5 these differences are shown to be independent of uniform vertical displacements of the constructed base line such as would occur if each P wave were raised or lowered a constant distance from the true base line by the preceding U wave.

It might next be wondered whether there is an alternating vertical displacement of the constructed base line resulting from superposition of alternate P waves on varying U waves. Assume, for example, that the P wave of the normal complex initiates on the true base line while the P wave of the blocked complex is raised above the true base line by the preceding U wave. In this case the constructed straight base line for both the normal and the blocked complexes will rest on the true base line at one end of the complex and will be elevated above it a certain constant distance at the other end. Therefore, the error in area measurements of alternating block resulting from this type of misplacement of the base line would be equal in amount for both types of complexes, and, consequently, the difference between the measured areas would still be the correct difference.

Some increase in the accuracy of the area measurements could have been obtained by adjustments of the straight constructed base lines in a manner similar to that described for some complexes from the dog experiment of Wilson and associates. However, a sufficient number of complexes have been studied to permit averages for each type of complex from each lead to be obtained, thus making such adjustments unnecessary. The magnitude of the cardiac complex area vector for the blocked complexes is slightly less than half that for the normal complexes. The ventricular gradient area difference vector is directed rightward, anteriorly and slightly inferiorly.

For the normal tracing the cardiac complex area vector can be considered to consist of three component vectors, the atrial gradient area vector and the right and left ventricular gradient area vectors. Thus,

$$A_P + A_{Ta} + A_{QRS_{RV}} + A_{TU_{RV}} + A_{QRS_{LV}} + A_{TU_{LV}} = G_A + G_{RV} + G_{LV} \quad (3)$$

where A_P, $A_{QRS_{RV}}$, $A_{QRS_{LV}}$ are the area vectors for atrial and right and left ventricular depolarization, A_{Ta}, $A_{TU_{RV}}$, $A_{TU_{LV}}$ are the area vectors for atrial and right and left ventricular repolarization, and G_A, G_{RV}, G_{LV} are the gradient area vectors for the atria and the right and left ventricles, respectively.

Following the onset of left bundle branch block the normal left ventricular QRS and TU area vectors become blocked left ventricular QRS and TU area vectors, whereas the left ventricular gradient area vector will be unchanged if Wilson's hypothesis holds. Thus,

$$A_P + A_{Ta} + A_{QRS_{RV}} + A_{TU_{RV}} + A_{QRS_{LV_{LBBB}}} + A_{TU_{LV_{LBBB}}} = G_A + G_{RV} + G_{LV_{LBBB}} \quad (4)$$

where $G_{LV_{LBBB}}$ is the left ventricular gradient area vector in the presence of left bundle branch block.

Subtracting (3) from (4) yields

$$A_{QRS_{LV_{LBBB}}} + A_{TU_{LV_{LBBB}}} - A_{QRS_{LV}} - A_{TU_{LV}} = G_{LV_{LBBB}} - G_{LV} \quad (5)$$

where either side of the equation is equal to the left ventricular gradient area difference vector obtained by subtracting the cardiac complex area vector for the normal complexes from that for the blocked complexes.

It may be that Wilson's hypothesis does not hold and that the left ventricular gradient is changed by alteration of left ventricular depolarization. On the other hand, Wilson's hypothesis may be valid, in which case the finite difference vector is presumably due to alterations of the lead fields secondary to altered ventricular depolarization.

INTERMITTENT WOLFF-PARKINSON-WHITE SYNDROME

Vectorcardiograms for the plane of the limb leads are derived in Fig. 6. Subtraction of these loops yields the difference vectorcardiogram shown in Fig. 7,*C*, from which the ventricular gradient area difference vector is derived in *D*. This difference area vector is obtained more directly in *E* and *F* from the measured areas of the electrocardiographic cardiac complexes.

SUMMARY

The concept of a mean vector with respect to time for a certain time interval is discussed. A simple method for determining the area vector for electrocardiographic cardiac complexes is presented, and the theoretical and practical advantages of its use are discussed. The ventricular gradient area difference vector is defined and is determined for the dog experiment of Wilson and associates, for two cases of right and two cases of left intermittent bundle branch block and for one case of intermittent anomalous atrioventricular excitation. It is pointed out that in each case this difference vector may be due to alteration of the lead fields or may be an indication of invalidity of Wilson's hypothesis.

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Renal Influence in Experimental Cardiac Necrosis

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Certain corticoid hormones and electrolytes when administered simultaneously to experimental animals are known to produce myocardial lesions, the "electrolyte-steroid-cardiopathy with necrosis" (ESCN).[1] It was shown that both the glucocorticoid and mineralocorticoid activities are necessary for this cardiotoxic effect. When either a pure glucocorticoid or a pure mineralocorticoid alone is injected simultaneously with a sensitizing salt (e.g., Na_2HPO_4), no cardiac necrosis occurs.[2] On the other hand, the presence of an ischemic kidney in the animal has an effect very similar to that of desoxycorticosterone (DOC), a pure mineralocorticoid compound that, when injected together with NaCl, produces the so-called "electrolyte-steroid-cardiopathy with hyalinization" (ESCH). The "endocrine kidney technique," introduced by Selye,[3] enables the kidney to arrest its excretory function and to act purely as a secretory organ, producing substances that cause hypertension, hyalinization of vessels, nephrosclerosis, and generalized periarteritis nodosa.[4] All these changes are also characteristic of the ESCH. The striking similarity between the manifestations of overdosage of DOC and those of the nonexcreting kidney moved us to seek further information about the physiologic characteristics of the substances liberated from the ischemic (or endocrine) kidney, in regard to their cardiovascular effect.

The three main problems were as follows: (1) Would the presence of an endocrine kidney, which normally causes the ESCH, condition for an ESCN-like cardiac lesion when employed instead of a potent mineralocorticoid in the course of a typical necrosis-producing treatment? (2) Do the ESCN-sensitizing salts change the cardiotoxic and angiotoxic effects of the ischemic kidney? (3) Is the role of the endocrine kidney in experimental cardiopathies specific or is it a mere nonspecific stress effect? In order to answer these questions we performed experiments on three series of rats.

MATERIALS AND METHODS

In all the experiments we used female Sprague-Dawley rats from the Quebec Breeding Farm, with an average initial body weight of 140 grams (range: 130 to 150 grams). The animals

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were kept on "Purina Fox Chow" and tap water ad libitum. Endocrine kidneys were produced, according to Selye,[3] by partial ligature of the aorta between the two renal arteries, using the stylet of a 22-gauge hypodermic needle, followed by ligation and transection of the left ureter at 0.5 cm. from the renal pelvis. Cold baths consisted in immersion in water at 0°C. for 3 minutes, twice daily. Motor denervation was performed by cutting the motor nerves of the four extremities. Restraint consisted in tying the rats to a board by the four limbs for 17 hours. Triamcinolone (Lederle) was injected subcutaneously once daily at the dose of 650 μg suspended in 0.2 ml. of water. Na_2HPO_4 (Reagent, Fisher) was administered by stomach tube twice daily at the dose of 2 mM. (284 mg.) dissolved in 4 ml. of water. On the fifth day of the experiments the surviving rats were killed with chloroform, and the hearts were examined with a magnifying glass to detect macroscopically visible necroses. The ultimate evaluation was made, however, after histologic examination. For this purpose the hearts were fixed with 10 per cent formalin solution, neutralized with $CaCO_3$, embedded in paraffin, and stained with hematoxylin-phloxine. The severity of the myocardial necroses is expressed in an arbitrary scale of 0 to 3, 1 being the smallest histologically detectable muscle-fiber destruction, and 3 standing for very extensive necrotic foci, also visible macroscopically.

RESULTS

First Experiment.—In the first experiment, 28 rats were divided into three groups and treated as indicated in Table I. We used triamcinolone as a corticoid, because it is a highly active pure glucocorticoid that is devoid of any cardiotoxic effect even if given with a sensitizing Na-salt and stress. We thought that if this hormone in combination with the endocrine kidney produced marked cardiac necrosis, it would suggest that the secretory products in this kidney have a mineralocorticoid-like effect. Much to our surprise, a very high incidence of severe necrosis occurred even in the phosphate-treated, endocrine-kidney bearing group and was similar to that of the rats receiving additional triamcinolone injections.

Second Experiment.—In the second experiment, we wanted to investigate the modifying effect of Na_2HPO_4 on the typical ESCH-producing action of the endocrine kidney. Thirty rats were divided into three equal groups and treated as indicated in Table II. In these animals, the typical hyalinizing and periarteritis-producing effect of the endocrine kidney was absent, since the ESCH is a rather chronic type of manifestation, and the experiment was of short duration. Despite the 50 per cent incidence of necroses in Group 1, in all cases the necrotic areas were limited to one or two muscle fibers only, with mild cellular reaction.

TABLE I. HUMORAL CONDITIONING FOR THE CARDIOTOXIC EFFECT OF THE ISCHEMIC KIDNEY

GROUP	NUMBER OF RATS	TREATMENT*	CARDIAC NECROSIS		MORTALITY (%)
			SEVERITY (0-3)	INCIDENCE (%)	
1.	8	Triamcinolone	0.1 ± 0.1	12.5	65
2.	10	Na_2HPO_4	2.1 ± 0.34	89	100
3.	10	Triamcinolone + Na_2HPO_4	1.9 ± 0.38	80	100

*In all groups, left renal ischemia was produced on the first day of the experiment.

In Group 2, the phosphate alone produced no change in the heart. However, the administration of the phosphate in Group 3 potentiated the otherwise very mild necrosis-eliciting effect of the ischemic kidney. In this group, all the animals except one succumbed with very severe and extensive cardiac necrosis, as shown in Fig. 1. This increased necrotizing action was not accompanied by an enhanced hyalinizing capacity. Hence, the sodium phosphate not only potentiated but also modified the typical action of the ischemic kidney.

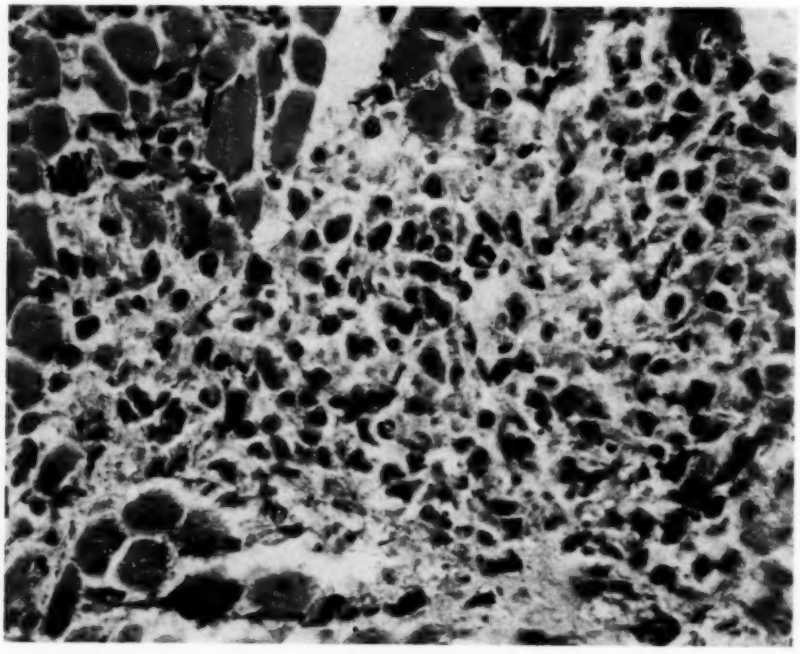

Fig. 1.—Necrotic focus in the myocardium of a rat bearing an endocrine kidney and treated with Na_2HPO_4 (hematoxylin-phloxine; ×400, reduced ⅓).

TABLE II. MODIFICATION BY Na_2HPO_4 OF THE CARDIOTOXIC EFFECT OF THE ENDOCRINE KIDNEY

GROUP	TREATMENT	CARDIAC NECROSIS		MORTALITY (%)
		SEVERITY (0-3)	INCIDENCE (%)	
1.	Endocrine kidney	0.7 ± 0.27	50	10
2.	Na_2HPO_4	0	0	0
3.	Endocrine kidney + Na_2HPO_4	2.1 ± 0.32	90	90

Third Experiment.—In the third experiment, the effect of the endocrine kidney was compared with that of some well-known stressors, since it was known already[5] that stress plays an important role in eliciting myocardial lesions, especially in combination with hormones and sensitizing electrolytes. Twenty-nine

TABLE III. COMPARISON BETWEEN THE EFFECT OF THE ISCHEMIC KIDNEY AND THAT OF SOME NONSPECIFIC STRESSOR AGENTS ON THE HEART

GROUP	NUMBER OF RATS	TREATMENT*	CARDIAC NECROSIS		THYMUS (MG.)	ADRENAL (MG.)	LOSS OF BODY WEIGHT (GM.)	MORTALITY (%)
			SEVERITY (0-3)	INCIDENCE (%)				
1.	10	Motor denervation	0.2 ± 0.2	10	53.4 ± 5.1	41.6 ± 4.1	32	30
2.	10	Cold bath	0.4 ± 0.17	40	76.2 ± 6.7	50.1 ± 1.4	29	29
3.	9	Endocrine kidney	2.1 ± 0.27	100	71.0 ± 5.5	32.9 ± 4.0	43	100

*In addition to the treatments listed above, all the rats were treated with triamcinolone and Na_2HPO_4.

rats were divided into three groups, and the treatment and results are shown in Table III. The weight of the thymus and adrenal glands, as well as the loss of body weight, are indicators of the degree of stress. It was previously shown that triamcinolone fails to condition for the necrotizing effect of the cardiotoxic Na-salts, even when the animal is simultaneously subjected to a very severe stress that normally produces extensive cardiac necrosis when applied concurrently with a hormone possessing both glucocorticoid and mineralocorticoid properties. In our experiment, the ineffectiveness of triamcinolone was confirmed in the case of motor denervation and cold baths (the two most potent stressors in eliciting the ESCN). All of the rats bearing an endocrine kidney, however, died with severe cardiac necrosis on the third and fourth day of treatment. This, together with the weights of the thymus and adrenal glands, and body weight (which show no significant differences among the groups), is contrary to the supposition that the endocrine kidney would exert its necrotizing effect merely through a nonspecific mechanism.

For further confirmation along these lines, we performed a small complementary experiment to elucidate the role of the ischemic kidney in connection with nonspecific mechanisms and time relationship. We wanted to compare the role of acute stress and that of the endocrine kidney in eliciting cardiac necrosis in the sensitized rats. As mentioned previously, acute stress is capable of producing myocardial damage in animals pretreated with electrolyte plus steroid[6]; hence, it was interesting to see whether the ischemic kidney possesses a similar nonspecific action within a very short time, when the typical cardiotoxic effects of this kidney cannot be manifested. Three groups of rats (5 animals in each) were treated with triamcinolone plus Na_2HPO_4 for 2 days. The first group served as controls, the second was restrained, and the third underwent the endocrine-kidney operation on the third day. Seventeen hours after the interventions, all the rats were killed. Microscopic examination revealed no myocardial necrosis in Group 1. The severity of the lesions in Group 2 was 1.4 ± 0.4, and in Group 3, it was 0.2 ± 0.2. Thus, the endocrine kidney was completely ineffective in this particular arrangement, in which the short duration of the experiment did not permit the kidney to exert any structural damage in the heart.

DISCUSSION

The presence of a nonexcreting ischemic kidney in the organism is known to produce hyalinizing and periarteritic cardiovascular changes, with some mild degree of necrosis of muscle fiber after 2 or 3 weeks. The additional administration of Na_2HPO_4 elicits extensive, macroscopically visible myocardial necroses within 3 days. On the other hand, this salt does not possess any sensitizing effect in regard to the hyalinizing type of changes. Furthermore, previous experiments demonstrated that Na_2HPO_4 together with hormones exerting both glucocorticoid and mineralocorticoid activity produces marked necrosis in the heart. In this respect, the endocrine kidney can substitute for the corticoid effect.

It is difficult to determine whether the nonspecific effect of an endocrine kidney plays a role in the mechanism of the electrolyte-produced cardiac necrosis.

The effectiveness of the stressor agents was recorded on the basis of the changes in weight of the thymus and adrenal glands, and the changes in body weight. According to these, the presence of an endocrine kidney was not more stressful than the other noxious agents, which, nevertheless, were devoid of any cardiotoxic effect. This indicates that the endocrine kidney has a rather specific role in the production of cardiac necrosis. Whether its mode of action is similar to that of the corticoids is not yet clear. In the production of the ESCN, the Na-ion has a crucial position.[7] According to current theories, the extracellular and intracellular shift of the Na and the K ions is the main cause of the cardiovascular damage. The ischemic kidney is also known to produce such ionic changes.[8,9] It was also observed[10] that DOC and the ischemic kidney produce identical electrolyte changes in the blood and in the arterial walls. It is possible that the cardiotoxic effect of certain corticoids and that of the ischemic kidney both act through the same electrolyte shift. It is interesting to note that Na_2HPO_4 modifies not only the effect of the endocrine kidney but also that of DOC; in both cases, an ESCN instead of an ESCH results, although the lesions resulting from DOC are less severe. On the other hand, the endocrine kidney acts similarly to the corticoids that condition the heart for the cardiotoxic effect of certain electrolytes.

Further studies are needed to reveal the relationship between the endocrine kidney and other electrolytes that sensitize or desensitize for myocardial necrosis, and to determine whether the cation and the anion are equally important components of the sodium salt. To date, we may conclude that Na_2HPO_4 can potentiate and modify the cardiovascular action of a kidney that exerts a selective secretory function. The substance or substances secreted by such a kidney act similarly to the corticoid hormones in regard to their conditioning effect for cardiac necrosis.

SUMMARY

The ischemic (or endocrine) kidney is known to produce hyalinizing cardiovascular lesions. Na_2HPO_4—a sensitizing salt for the production of the "electrolyte-steroid-cardiopathy with necrosis" (ESCN)—can change this hyalinizing effect to a necrotizing one, in the rat.

The effect exerted by the endocrine kidney in this respect is identical to that of the corticoids that condition for the cardiotoxic action of certain Na-salts, such as Na_2HPO_4.

The ischemic kidney apparently does not act as a nonspecific stressor, since similar, otherwise strongly damaging agents are unable to condition for the phosphate-induced cardiac necrosis, whereas the signs of the alarm reaction (changes in weight of the adrenal and thymus glands, changes in body weight) are of equal intensity both in the stressed animals and in those bearing an ischemic kidney.

The possible relationship between the ischemic kidney, electrolytes, and corticoids in the production of myocardial lesions is discussed.

The author gratefully acknowledges generous supplies of triamcinolone from Lederle Laboratories.

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Case Reports

Anomalous Left Coronary Artery. Adult Type

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A machinery type of murmur at the base of the heart is not always caused by a persistent ductus arteriosus.[1-3] Among several cardiovascular disorders accompanied by a continuous murmur, coronary anomalies should also be considered.[4] By means of aortography, with the tip of the catheter placed in the ascending aorta, anatomic derangements of the coronary vessels can be visualized in the living patient.[5]

CASE REPORT

A school physician happened to observe an organic heart murmur in a 16-year-old school boy. The boy's mother had not been ill during pregnancy, and the boy's birth (twin birth) and physical development had been uneventful. He never had complained of exertional angina; for a year he had been troubled with only slight dyspnea after great exertion.

The patient was a normally developed, healthy-looking boy. Inspection and palpation of the region of the heart revealed no abnormalities. Blood pressure was 120/70 mm. Hg. A Grade 2 continuous murmur could be heard with maximal loudness in the second intercostal space on the left of the sternum (Fig. 1). The electrocardiogram showed hypertrophy of the left ventricle (Fig. 2). On fluoroscopy, the heart shadow seemed moderately enlarged, mainly to the left. The phenomenon of hilar dance could not be demonstrated. During catheterization studies we obtained normal pressure curves from the right side of the heart. Repeatedly, a slight increase in the oxygen content (0.5 vol. per cent) of the main pulmonary artery was found, as compared with the oxygen content of the right ventricle. A left-to-right shunt of approximately 2 liters per minute was computed. All attempts to reach the aorta with the tip of the catheter failed. Nevertheless, we decided that the most probable diagnosis in accordance with most of the more important findings was a patent ductus arteriosus, and surgical intervention was advised.

During the operation (Aug. 18, 1955) no patent ductus arteriosus was found, but the surgeons* felt a definite thrill at the root of the main pulmonary artery. A large opening in the pericardial sac was made, but no abnormalities could be observed at the outside of the heart. The thorax was closed again, no correct diagnosis having been made.

Renewed catheterization studies again showed a slight increase in the oxygen content of the main pulmonary artery (0.5 to 0.75 vol. per cent). To our surprise, at angiocardiography, an abnormally long, tortuous, and dilated right coronary artery became visible. The left coronary artery, however, appeared to be absent.

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By means of selective aortography, with the tip of the catheter in the ascending aorta, we tried to study the anatomy of the coronary arteries in this patient (Figs. 3-8). The origination of the left coronary artery from the aorta was absent. The right coronary artery originated at the normal place from the aorta, but was abnormally dilated and tortuous. After that, in the posteroanterior view, an area of anastomoses became visible in the wall of the left ventricle (Fig. 3). After having passed these anastomoses the contrast medium was collected in several small branches, which, as to localization and branching, corresponded completely with the branches of the left coronary artery in a normal person (Figs. 4, 5, 7). Eventually the contrast medium became visible, both in the posteroanterior and the lateral views (Figs. 4, 7), at the site of the pulmonary artery.

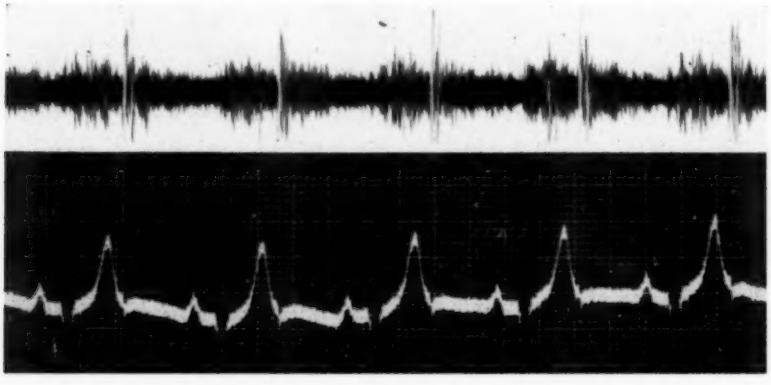

Fig. 1.—Phonocardiogram recorded in the second left intercostal space, and standard lead II.

In our opinion, these findings are entirely in accordance with what may be expected in a case of anomalous left coronary artery in which the left coronary artery originates from the pulmonary artery, and in which there is a reversed direction of the blood stream in this left coronary artery. As far as we know, this is the first time that, by means of aortography during life, a connection between aorta → right coronary artery → anastomotic network → left coronary artery → main pulmonary artery could be demonstrated.

DISCUSSION

Abnormal origin of one or both coronary arteries has been repeatedly described in the literature. It is possible that both coronary arteries originate from the pulmonary artery, a situation with is incompatible with life.[3,6] The origination of the right coronary artery from the pulmonary artery has rarely been described; in one case it concerned an unexpected finding at autopsy of a patient who had never had complaints. Origination of the left coronary artery from the pulmonary artery has been much more frequently described, predominantly in very young children, but also in adults. In a recent publication, most of the reported adult cases from the literature are reviewed.[7]

One gets the strong impression that clinically a sharp distinction should be made between the two types.[8] The infantile type, also referred to as the Bland-White-Garland syndrome, is attended with anginal discomfort, an anterior infarction pattern electrocardiographically, enlargement of the heart shadow, and, usually within one year after birth, a lethally developing left heart failure.[3] On the other hand, in the adult type there are frequently no complaints at all during life, and diagnosis is sometimes an accidental finding at autopsy of a

patient who died unexpectedly after great exertion.[8] Hence, very little is known about the clinical features in the adult type of anomalous left coronary artery.[7]

It is worth mentioning that our patient had no complaints. Key points in the clinical diagnosis in this case were: the classic machinery type of murmur, the left-to-right shunt at the level of the main pulmonary artery, and the failure of the catheter tip to reach the aorta via the suspected patent ductus. If this combination of symptoms presents itself, one has to consider the existence of anomalies other than the quite obvious persistent ductus arteriosus.

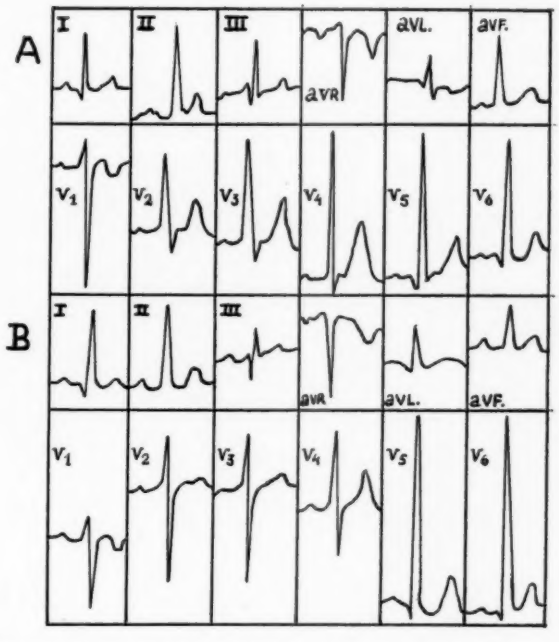

Fig. 2.—Electrocardiograms recorded (*A*) before thoracotomy, and (*B*) one year after operation (unsuccessful).

Murmur.—Judging from the experiences with our patient during operation, the murmur probably arises at the site of entrance of the left coronary artery into the pulmonary artery; this site is at about the same place as that at which the murmurs of a patent ductus arteriosus arise. Therefore, no distinction can be made on the ground of localization or conduction of the murmur. The character of the murmur in the case of the anomalous left coronary artery in our patient was also completely similar to that of a patent ductus arteriosus. Moreover, one has to bear in mind that many anomalies give rise to a continuous murmur.[1-3] Finally, it should be mentioned that—as is also true with patent ductus arteriosus—a continuous murmur was not observed in all cases of anomalous left coronary artery.[7]

Radiology.—Radiologic procedures appeared to make a considerable contribution to the diagnosis. Angiocardiography aroused suspicion of a coronary anomaly, because we could not detect a contrast-filling of the left coronary artery, and the right coronary artery was malformed. Direct "coronariography," with the tip of the catheter in the ascending aorta, provided us with a clear picture of

Fig. 3.

Fig. 4.

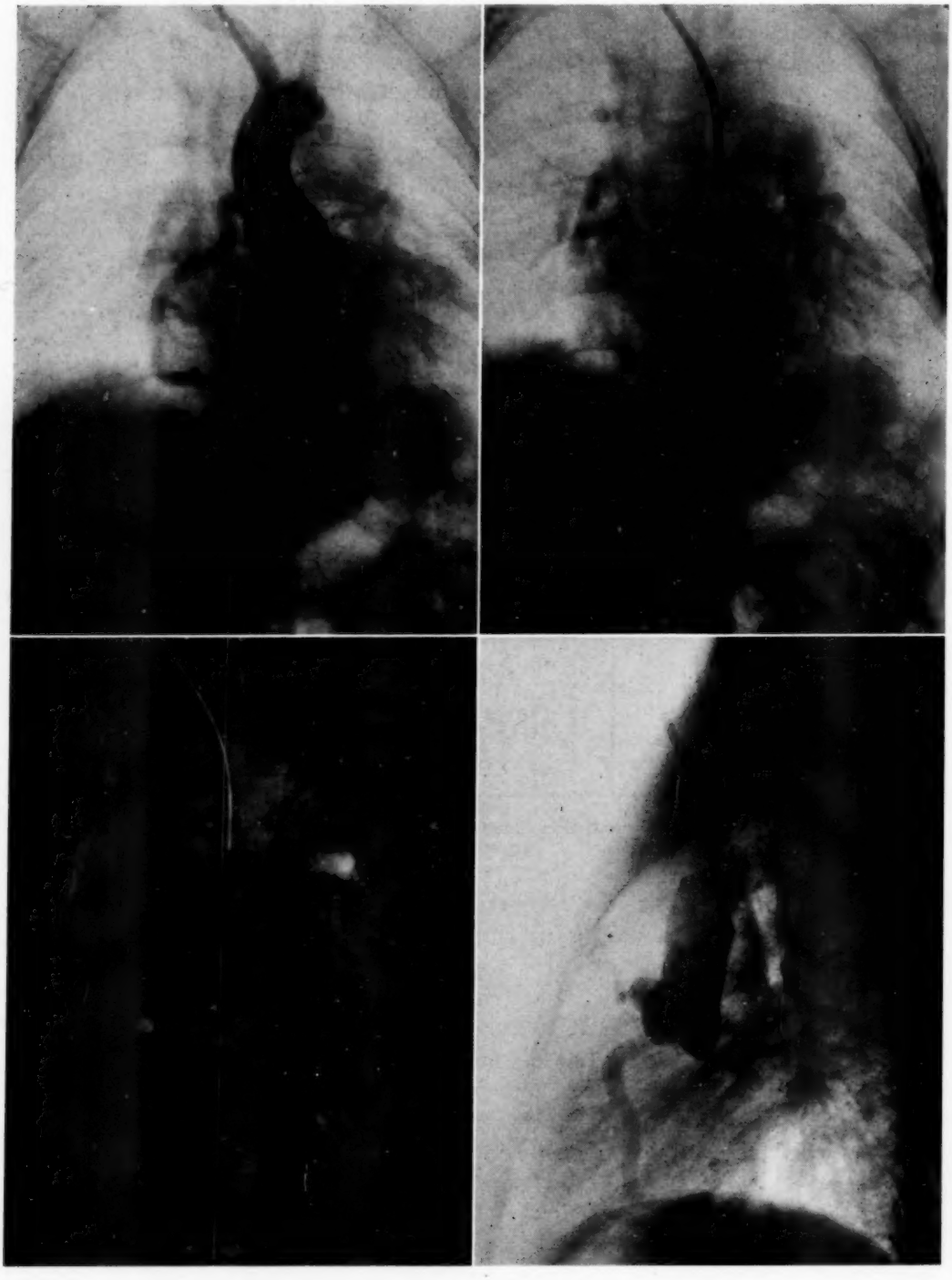

Fig. 5.

Fig. 6.

Figs. 3-6.—*(For legends see opposite page.)*

the anomaly. We are of the opinion that the appearance ultimately of contrast medium at the entrance of the left coronary artery into the main pulmonary artery gives very strong evidence for the diagnosis of anomalous left coronary artery. This appears also to be in accordance with the conception of Edwards[9] and the postmortem perfusion results of Case, et al.[10] This conception is merely based upon indirect arguments and autopsy techniques. We believe that our aortograms support a definite and direct argument in the living patient in favor of the aforementioned conception.

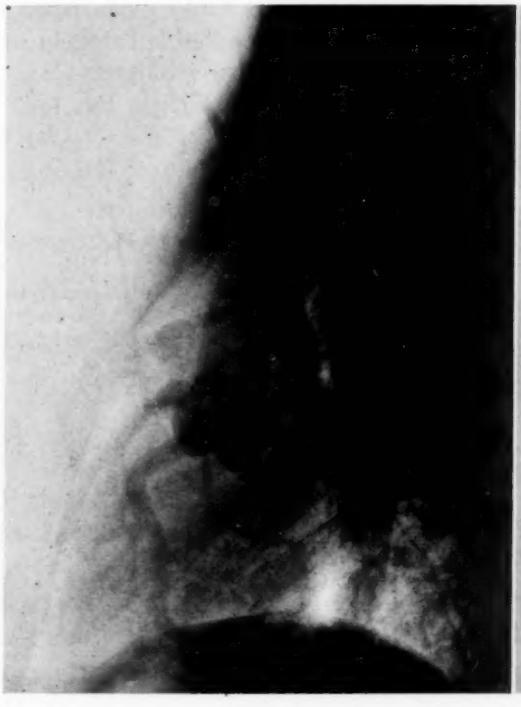

Fig. 7.

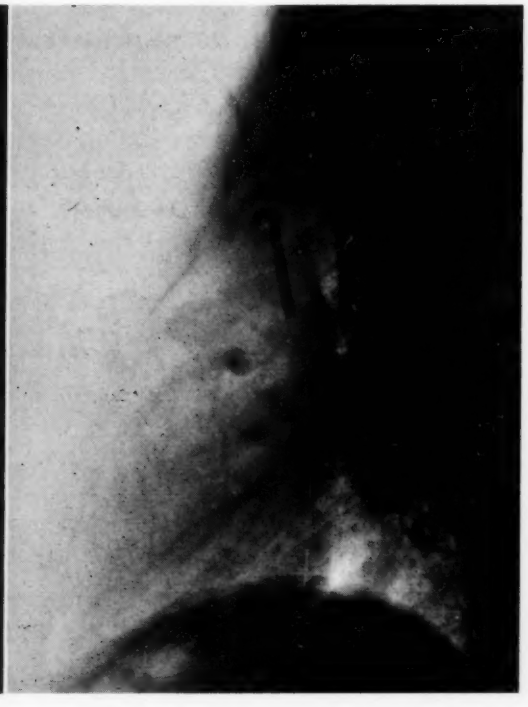

Fig. 8.

Fig. 7.—Aortography, lateral view II: one second later, several branches corresponding to the branches of the left coronary artery in a normal person are filled with contrast medium. The contrast is ejected beside the aorta at the site of the pulmonary artery. The contours of this ejected contrast medium suggest a jet against the opposite wall of the pulmonary artery.

Fig. 8.—Aortography, lateral view III: one second later, contrast medium has disappeared from the right coronary artery. Note the concentration of contrast medium in the pulmonary artery.

Fig. 3.—Aortography, posteroanterior view I: the contrast medium fills the aorta, the dilated right coronary artery, the anastomotic network, and is passing through branches of the left coronary artery to the main pulmonary artery on the left of the aorta. Note the absence of the left coronary artery from the aorta.

Fig. 4.—Aortography, posteroanterior view II: one second later, the branches of the left coronary artery are filled with contrast medium. A large circle of contrast medium is visible on the left of the aorta, at the site of the pulmonary artery. Contrast medium is also visible in the branches of the pulmonary artery in both lungs.

Fig. 5.—Composition of both Figs. 3 and 4 by the subtraction method (Prof. Ziedses des Plantes).

Fig. 6.—Aortography, lateral view I: the contrast medium fills the aorta, the right coronary artery, and several branches of the anastomotic network. A smaller branch, near the origin from the aorta, is probably the (dilated) pulmonary conus branch.

For the surgeon it is important to know of the various causes for a faulty diagnosis of patent ductus. The persistence of a continuous murmur after successful ligation of a patent ductus arteriosus will very rarely be based on the simultaneous occurrence of a patent ductus and an anomalous left coronary artery.[6,7] In our opinion, the surgeon will occasionally be surprised not to find the suspected patent ductus. In a number of cases, opening of the pericardial sac will bring the diagnosis of a coronary anomaly to light.[11-13] However, in the case of our patient, two experienced heart surgeons did not see any abnormality at the outside of the heart, so that the operation—because the true diagnosis had not been suspected—was concluded with nothing achieved. In retrospect, we have to assume that the anastomotic network had been embedded deeply in the myocardium.

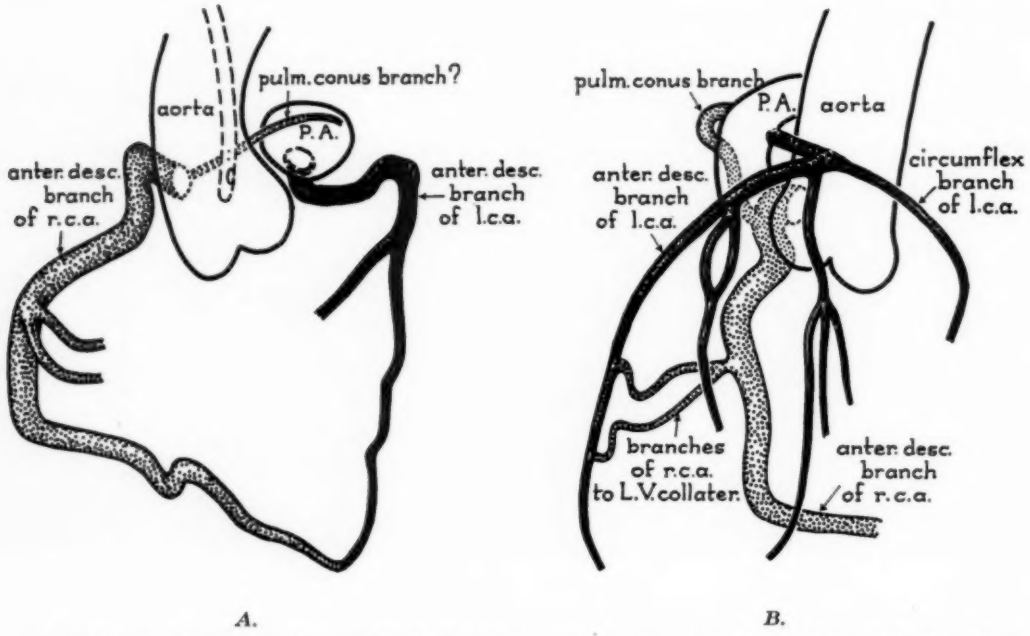

Fig. 9.—*A*, The anatomic anomaly in the posteroanterior view. *B*, The same as *A*, in the lateral view. *Dotted vessels:* right coronary artery and its branches. *Dark vessels:* left coronary artery and its branches. (Compare diagrams of normal persons: di Guglielmo et al.[5]

Does the diagnosis, adult type of anomalous left coronary artery, also imply therapeutical consequences? In answering this question, one has to bear in mind that, according to our experience, and data from the literature, these patients usually have no complaints. In the majority of reported cases, patients unexpectedly succumbed after great bodily exertion; the age at the time of death varied from 16 to 64 years.[7] The left-to-right shunt, although small, means an overloading of the left ventricle, and in our 16-year-old patient it had already led to a hypertrophy pattern of the left heart on the electrocardiogram and radiologic enlargement. It may be expected, therefore, that at least in some cases complaints will arise in the long run, and that every patient with this anomaly is always threatened with sudden death during great exertion. Ligation

of the abnormally originating coronary artery near its (functional) entrance, i.e., (anatomic) origin from the pulmonary artery, is a very defensible procedure from a theoretical point of view. If ligation of this abnormal artery does not cause any deleterious effects during operation (e.g., ECG derangements), and especially if myocardial color and tone is improving (as was the case with the patient of Dr. Edgar W. Davis, cited in Reference 10), such ligation of this artery seems indicated. By doing this, one abolishes the extra burden to the left ventricle, and probably—what is more important—one succeeds in stopping the leakage of well-oxygenated blood from the right coronary artery to the pulmonary artery, stimulating in this way a normal removal of venous blood via the capillaries of the muscle of the left heart to the coronary sinus. It seems to us that this will favorably influence the oxygenation of the wall of the left ventricle.

As yet, our patient unfortunately has refused to undergo a re-thoracotomy which we advised in order to ligate the anomalous left coronary artery. Up till now the patient has no complaints and enjoys good health. Very interesting is the fact that our patient has a twin brother (at first glance: identical twins!) who also has an organic heart murmur. Unfortunately, we could not persuade him to undergo a thorough examination.

SUMMARY

In a 16-year-old boy without complaints a persistent ductus arteriosus was diagnosed. The diagnosis was based mainly on a typical continuous murmur. During the operation no such anomaly was found. Reinvestigation by means of selective aortography revealed an anomalous left coronary artery emptying into the pulmonary artery. The proof of the diagnosis is considered to be the appearance of contrast medium in the pulmonary artery after passage through the anomalous left coronary artery. These aortograms are presented, and on the basis of the combination of several, in themselves a specific phenomenon, the diagnosis can be suspected. Ligation of this abnormally originating artery near its entrance in the pulmonary artery is proposed.

We are indebted to C. A. Jansen, M.D., chief radiologist of Onze Lieve Vrouwe-gasthuis, for his invaluable assistance in performing the aortography, and to Prof. B. G. Ziedses des Plantes, Department of Radiology, University of Amsterdam, for his cordial help in creating Fig. 5 by means of the subtraction method.[14]

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Bilateral Bundle Branch Block

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Bilateral bundle branch block is rarely diagnosed in clinical electrocardiography,[1-9] even though lesions of both branches of the common bundle are frequently noted on histologic examination. It is a well-recognized fact that bilateral bundle branch block of a stable nature cannot be differentiated from the effect of blocking lesions in the A-V node or in the common bundle. Complete A-V block may be caused by a lesion in the A-V node or in the common bundle, but it can also be the result of interruption of conduction in both the right and the left bundle branches. Prolongation of the P-R interval in conjunction with the pattern of right or left bundle branch block may be the effect of two independent lesions: one lesion, situated above the bifurcation of the bundle in either the main bundle or the A-V node, causes the prolongation of the P-R interval; the other, located in one of the bundles, produces the bundle branch block pattern. An electrocardiogram of this kind may also be produced by lesions in each of the branches, when the degree of impairment of conduction differs in the branches. The sinus impulse travels faster in the branch with the lesser disturbance and reaches the contralateral branch in advance of the impulse traveling in the latter. The prolongation of the P-R interval expresses the delay in the bundle with the lesser disturbance.

In bilateral bundle branch block in which the degree of impairment is fluctuating, increasing and decreasing in one bundle beyond the severity of the disturbance in the contralateral bundle, in addition to changes in the P-R interval, alternating or intermittent changes in the contour of the QRS complex occur. It changes from the pattern of block of one bundle to the pattern of block of the contralateral bundle. In instances in which block in one bundle is permanent and complete, intermittent conduction delay in the other bundle can only be recognized as such when the resulting prolongation of the P-R interval is associated with a change in the contour of the QRS complex. Theoretically, for such a change to occur, the region of the partial block must extend into a subdivision of the bundle branch. The delay in the excitation of the ventricular muscle mass supplied by these junctional fibers causes a shift in simultaneously

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†Deceased.

activated parts of the left and right ventricle and, consequently, a change in the contour of the QRS complex.

The case presented reveals transient block in one bundle in the presence of complete and permanent block in the other bundle branch.

CASE REPORT

B. H., an 83-year-old white man, was admitted to the Brooklyn Hebrew Home and Hospital for the Aged on May 1, 1957. His past history was noncontributory. He was asymptomatic on admission. The heart was not enlarged. On auscultation a soft apical systolic murmur was heard. The heart action was regular; the rate was 72 per minute. The heart sounds were of good quality. Blood pressure was 155/75 mm. Hg. Routine laboratory work-up did not disclose any significant findings. The electrocardiogram revealed sinus rhythm and right bundle branch block.

Course in Hospital.—In February, 1958, some changes in his mental condition were observed. Neuropsychiatric examination revealed a "chronic brain syndrome" with cerebral arteriosclerosis. On April 2, 1958, the patient sustained a cerebrovascular accident. He did not respond to treatment and expired the next day.

*Necropsy Findings**.—The myocardium was normal in appearance except for minimal streaky fibrosis in the posterior left ventricular wall just below the ring and upper portion of the interventricular septum. The coronary arteries were sclerotic but had wide lumina.

Microscopically, the myocardium showed old patchy areas of fibrosis. The coronary arteries showed subintimal thickening.

Detailed Study of Electrocardiogram.—An electrocardiogram taken on Jan. 24, 1958, showed P waves of normal configuration, spaced regularly at intervals of 0.80 sec., corresponding to a rate of 75 per minute. The P-R interval was 0.20 sec. The QRS complexes were of the right bundle branch block pattern. On several occasions, changes in rhythm as well as in the contour of the QRS complexes occurred. The change in shape was accompanied in every instance by lengthening of the P-R interval from 0.20 to 0.24 sec. Such a change is illustrated in Fig. 1. The figure shows three successive groups of Wenckebach periods at a 3:2 ratio, followed by a period of 3:2 block without the Wenckebach phenomenon. The first beat in each group has the characteristic features of right bundle branch block, of the type observed in previous records in this case. The second beat in each of the Wenckebach periods is also of the right type, is identical in width, but is of quite a different shape. The R wave is small. The RS deflection is grossly slurred and its nadir is blunt.† The P-R interval lengthens from 0.20 sec. in the first beat to 0.24 sec. in the second beat.

Another example of the above-mentioned change is shown in Fig. 2. The tracing begins with three periods of 2:1 block. This is followed by three short groups of Wenckebach periods at a 3:2 ratio, and finally a period of 4:3 block. The first cycle in each group reveals the "usual" contour of QRS and is preceded by a P-R interval of 0.20 sec. The QRS complex of the subsequent cycle or cycles preceding a dropped beat is also of the right bundle branch block type, but differs in shape in that the R wave is smooth and higher and the S wave deeper. These complexes are of the "modified" contour. The change in the contour is accompanied by a prolongation of the P-R interval from 0.20 to 0.24 sec. In the third group, in which two complexes of the "modified" contour precede a dropped beat, the P-R interval does not show progressive lengthening but measures 0.24 sec. in both cycles. QRS complexes of the "usual" contour follow in a regular sinus rhythm in both illustrated instances. The P-R interval is invariably 0.20 sec.

Generally, it was observed that the QRS complex of the first cycle in each group, following a long diastolic pause, was of the "usual" contour, and in no instance of the "modified" contour. QRS complexes of the "modified" contour—whether appearing singly, or as consecutive beats—were always followed by a dropped beat and in no instance by a QRS complex of the "usual" contour.

***Autopsy performed by Dr. Herman Bolker.**

†For identification purposes, the QRS complex of the first cycle will be referred to as the "usual" contour of QRS, that of the second cycle as the "modified" contour.

DISCUSSION

In the sinus beats of the "usual" contour seen in Figs. 1 and 2, the impulse was blocked in the right bundle. The stimulus was conducted in the left bundle, and from there spread and activated both ventricles, giving rise to the right bundle branch block pattern. The A-V conduction time in these cycles measures 0.20 sec., which is accepted as the upper limit of normal. It follows that the im-

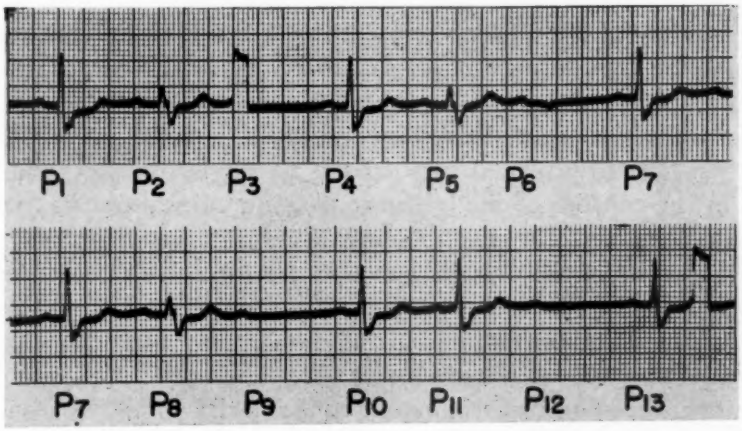

Fig. 1.—Continuous strip of Lead I. The last cycle in the upper row (*P7*) is repeated at the start of the lower row. Three Wenckebach periods are present at the start. The QRS of the first beat in each period is of the right bundle branch block type designated as the "usual" contour; the second QRS is also of the right bundle branch block type but differs in contour and is designated as the "modified" contour. The P-R of the first beat measures 0.20 sec. (*P1, P4, P7*), that of the second beat measures 0.24 sec. (*P2, P5, P8*). A period of 3:2 block follows (*P12* is blocked). The QRS of the first and second beats are of identical contour; the P-R measures 0.20 sec. in both cycles.

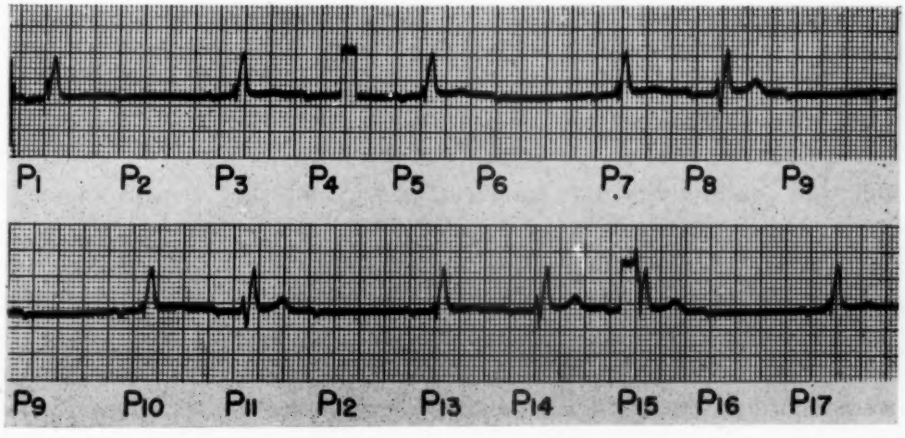

Fig. 2.—Continuous strip of Lead V_1. *P9* of the upper row is repeated at the start of the lower row. The tracing begins with three periods of 2:1 block (*P2, P4, P6* are blocked). The QRS complexes are of the right bundle branch block type. Three Wenckebach periods follow. The QRS of the first beat in each group is of the "usual" contour, that of the second beat in each group is of the "modified" contour. Then follows one period of 4:3 block (*P16* is blocked). The QRS of the first beat is of the "usual" contour, that of the second and third beats is of the "modified" contour. The change is associated with prolongation of the P-R interval from 0.20 to 0.24 sec. Regular sinus rhythm with QRS complexes of the "usual" contour follows; P-R is 0.20 sec.

pulse progressed at normal speed in the left bundle. Transient impairment of conductivity in the left bundle and in parts of its subdivisions causes lengthening of the P-R interval and changes the QRS complex to the "modified" contour. These effects have been produced experimentally. In the laboratory animal, severance of one bundle resulted in the bundle branch block pattern, and simultaneous compression of the contralateral bundle produced prolongation of the P-R interval and change in the contour of the QRS.[10] Apparently, complete interruption of conduction in the left bundle resulted in dropped beats in our case.

The possibility of a transient complete A-V block located in the A-V node or in the common bundle may be discarded for the following reasons: (1) The electrocardiographic tracings show that the blocked auricular impulses occur only in conjunction with other evidence of a conduction disturbance in the bundle branch. This suggests that the dropped beats and the prolongation accompanied by changes in the contour of the QRS are both manifestations of damage to the left bundle, and merely represent different degrees of the disorder. (2) The P-R interval of the cycles of the "usual" contour is invariably in the normal range of 0.20 sec. This argues against the presence of a conduction disturbance above the bifurcation of the common bundle. (3) The order in which the arrhythmia regresses in this tracing—as illustrated in Fig. 2—is also in keeping with the assumption of a receding disturbance in conductivity in the left bundle. When the depression in the left bundle is marked, only every second impulse is transmitted to the ventricles by way of the left bundle, apparently at normal speed. Following the three recorded periods of 2:1 block, conductivity improved somewhat, resulting in 3:2 block with the Wenckebach phenomenon. Further improvement led to 4:3 block. Following the dropped beat of the last group, the rhythm returned to that usually observed in this tracing. These findings are similar to those observed in the experimental production of bilateral bundle branch block. In the laboratory animal, complete A-V block appears as the immediate effect of severing one bundle branch and damage (compression) of the contralateral branch. With gradual recovery from compression, auricular impulses are passed on to the ventricles in decreasing block ratios. Blocks of the Wenckebach type were also observed during recovery from compression in these experiments.[10]

Delay in conductivity was transient at the time that the tracing shown in Figs. 1 and 2 was taken, lasting short periods of time. When the next electrocardiogram was taken—2 weeks later—the damage to the left bundle was presumably of greater severity. Every second impulse was blocked, and in spite of the long rest period produced by the 2:1 block, no recovery in conductivity took place. Only complexes of the "modified" contour associated with prolongation of the P-R were recorded. The last tracings, taken several weeks later, showed periods of complete A-V block alternating with periods of 3:1 and 2:1 block, suggesting progressive damage to the left bundle. This sequence of changes is the reverse of that observed in the first tracing, when the disturbance in the left bundle was apparently still reversible. It is also the reverse of the sequence observed in experimental bilateral bundle branch block, when compression of the contralateral bundle was released.

CONCLUSIONS

A case is presented showing evidence of bilateral bundle branch block. Permanent block was present in one bundle prior to the occurrence of bilateral bundle branch block; intermittent conduction disturbance in the contralateral bundle produced types of block analogous to those observed in animal experiments in which the experimental injury to the bundle is localized and transient. However, in our case this disturbance was progressive over a period of 3 months, indicating a damaging process of increasing severity.

It may be assumed that in this case the gradual narrowing of the supplying branch of a coronary artery, with the consequent increase in ischemia, is the basis for the progressive deterioration in conductivity in the left bundle. The case is of special interest since it demonstrates the rare instance in which the diagnosis of bilateral bundle branch block can be made in the presence of complete and permanent block in one bundle.

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Clinical-Pathologic Conference

James W. DuShane, M.D., William H. Weidman, M.D., Patrick A. Ongley, M.D., H. J. C. Swan, M.D., John W. Kirklin, M.D., Jesse E. Edwards, M.D., and Horst Schmutzler, M.D., Rochester, Minn.

DR. SCHMUTZLER: A 2-month-old white girl was admitted to the hospital in severe cardiac failure. Dr. DuShane, you saw this patient at her admission.

DR. DUSHANE: The mother's pregnancy was reported as being uncomplicated prior to the last 4 months, when she had experienced systemic hypertension. The patient was born at term after a normal labor. The birth weight was 6 pounds, 3 ounces. It was necessary to keep the infant in an incubator for 2 days after delivery because of irregular respiration; however, she improved and was dismissed to her home on the fifth day. At home, her parents noted rapid respiration, and easy fatigue with feedings. The cry was weak, and the face and hands became dusky with exertion. A severe cough developed at 5 weeks of age, and she was hospitalized with the diagnosis of pneumonia; a heart murmur was noted for the first time during this admission. The pneumonia improved with antibiotic therapy, and the patient was dismissed. At 2 months of age, it was necessary to rehospitalize her because of continued cough; she was given digoxin and was transferred to our care.

Our initial examination revealed a critically ill infant who was dyspneic and moderately cyanotic. The weight was 8 pounds. The blood pressure, taken by the flush technique, was 60 mm. Hg in the left arm and 45 mm. Hg in the left leg. The heart rate was 140 beats per minute and was regular. The heart was overactive. The first heart sound was normal and the second sound was narrowly split, with the pulmonary component moderately increased. A Grade 2, low-pitched, systolic murmur was heard best in the third and fourth left intercostal spaces, fading at the left second intercostal space and the apex; diastolic murmurs were not heard. Scattered crackling râles were present at the bases of both lungs, and the liver was palpable 3 cm. below the costal margin. The femoral pulses were easily palpable but not bounding.

From the Mayo Clinic, Rochester, Minn.

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DR. SCHMUTZLER: Dr. Weidman, do you have any additions to make?

DR. WEIDMAN: It was obvious that we were dealing with a critically ill infant in cardiac failure, probably complicated by pulmonary infection. Dr. DuShane, what is your interpretation of the electrocardiogram?

DR. DUSHANE: The electrocardiogram (Fig. 1) showed a mean QRS axis of +120 degrees, and vectorial analysis of the scalar electrocardiogram showed a clockwise QRS loop in the frontal plane. The P waves suggested atrial enlargement, and those leads representing the right ventricle indicated increased pressure in the right ventricle, probably equal to systemic pressure. Leads II, III, and aVF best represented the left ventricular potential and indicated overwork of the left ventricle. Dr. Ongley, can you comment on the thoracic roentgenograms?

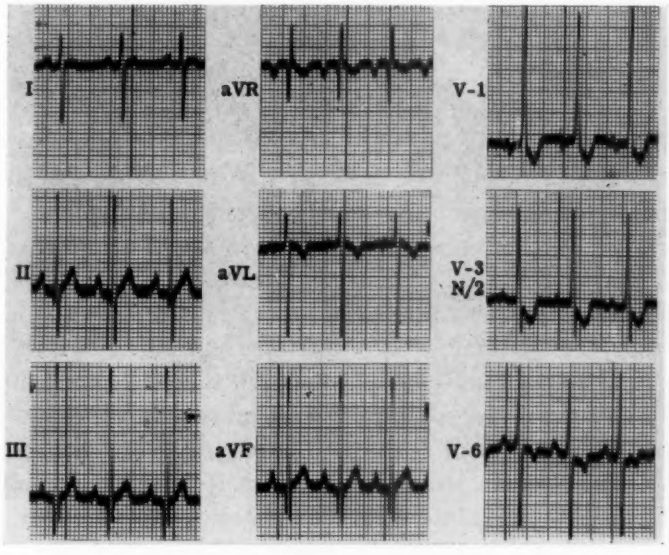

Fig. 1.—The electrocardiogram.

DR. ONGLEY: Roentgenographically, the heart appeared greatly enlarged. The cardiothoracic ratio was 65 per cent. The pulmonary vascular markings were increased, and a zone of increased density, probably of inflammatory origin, was present in the right upper lobe (Fig. 2).

DR. SCHMUTZLER: The use of digoxin was continued and, although the electrocardiogram demonstrated a digitalis effect, only slight improvement was noted clinically. A throat culture was made, and administration of penicillin and streptomycin was begun because of the possibility that the patient had an accompanying pulmonary infection; the culture disclosed the usual bacterial flora. Results of urinalysis were normal. The value for hemoglobin was 15.6 Gm. per 100 ml. of blood. The leukocytes numbered 7,900 per cubic millimeter of blood, with 15 per cent lymphocytes, 7 per cent monocytes, 73 per cent neutrophils, and 5 per cent eosinophils. Studies of palmar sweat did not indicate an increase in electrolytes. Dr. DuShane, in reading through the chart, I get the

impression that the patient did not respond well to the usual anticongestive measures.

DR. DUSHANE: That is true. Despite adequate digitalization, intermittent use of diuretics, and a low-sodium formula, the râles and the hepatomegaly persisted. During much of the time, the patient was extremely weak.

It was difficult to arrive at a definite clinical diagnosis. The patient obviously had a left-to-right shunt, with cardiac enlargement, increased pulmonary blood flow, and electrocardiographic evidence of overwork of the left ventricle and increased right ventricular pressure. The clinical diagnosis rested between a large ventricular septal defect and a patent ductus arteriosus. The cyanosis was worrisome, however.

DR. ONGLEY: The infant most certainly had a large left-to-right shunt; of course, we all have seen cyanosis in the presence of severe congestive heart failure. Cardiac catheterization was done in order to differentiate between a ventricular septal defect and a patent ductus arteriosus.

DR. SWAN: This small child was catheterized from the right arm without anesthesia. The catheter immediately passed through an aorticopulmonary communication, considered most likely to be a patent ductus arteriosus. The catheter could be passed into the left pulmonary artery, but it was never in the right pulmonary artery. When the child breathed 100 per cent oxygen, pressures of 80/35 and 60/36 mm. Hg were recorded in the aorta and pulmonary artery, respectively. When the patient breathed air, the pulmonary arterial pressure increased, so that the systemic and pulmonary pressures were essentially equal; the oxygen saturation of blood taken from the femoral artery at this time was 74 per cent. The data on the oxygen saturation of the blood indicated the presence of a left-to-right shunt of considerable magnitude when the child breathed oxygen, and a right-to-left shunt with a small left-to-right shunt when the child breathed room air. The laboratory diagnosis was a patent ductus arteriosus.

DR. KIRKLIN: In consultation, it appeared from the combined clinical and catheterization data that the diagnosis was a patent ductus arteriosus in an infant with severe cardiac failure. Although the child was critically ill, closure of a patent ductus arteriosus in such patients has not been associated with a high mortality rate, and it certainly appeared that closure of the ductus was advisable.

DR. SCHMUTZLER: Would the pediatric cardiologists like to comment at this time?

DR. DUSHANE: I can speak only for myself; however, in a situation such as this, with a critically ill infant unresponsive to a strict medical regimen carried out in the hospital over a 2-month period, I think that the only chance for survival would be closure of the patent ductus.

DR. ONGLEY: I most certainly would agree.

DR. KIRKLIN: A primary posterolateral incision was made on the left, and the thoracic cavity was entered through the bed of the nonresected fifth rib. The mediastinal pleura was opened over the upper part of the descending aorta, and the ductus arteriosus was dissected out. I could not palpate a definite thrill

over the heart itself, and I did not think it wise to open the pericardium. The great vessels appeared to be in normal position. A patent ductus arteriosus measuring 8 mm. in length and 5 mm. in diameter was present. It was definitely a large ductus for a baby of this size. The ductus was divided between appro-

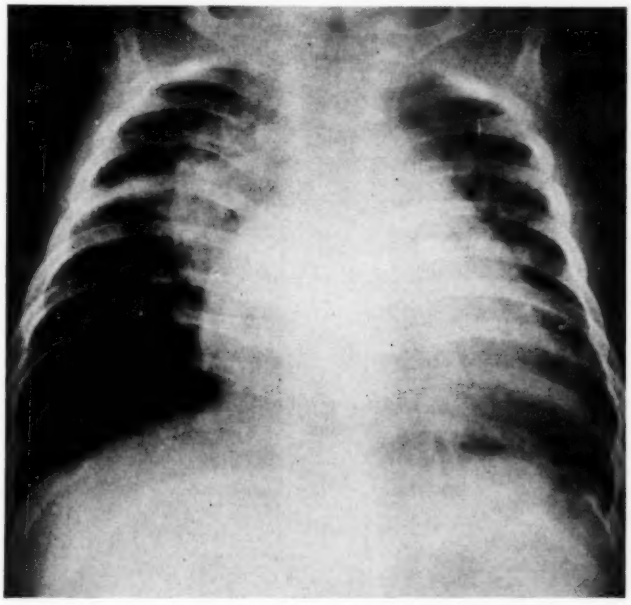

Fig. 2.—Posteroanterior roentgenogram of the thorax.

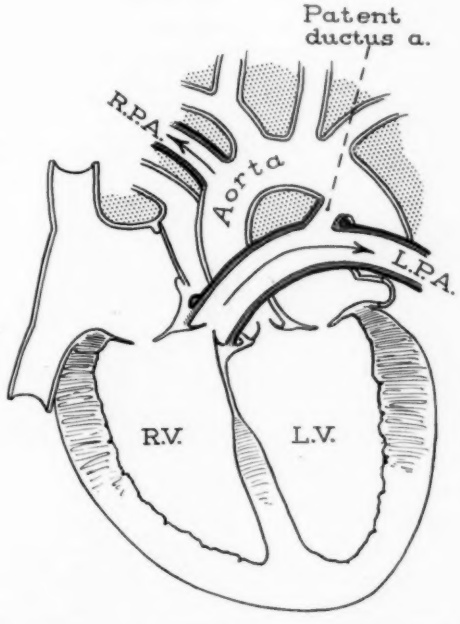

Fig. 3.—Diagram of central circulation. The right pulmonary artery arose from the aorta, and a left-sided patent ductus arteriosus was present. The pulmonary venous connections with the left atrium were normal.

priately placed Potts' fine-toothed clamps; the aortic and pulmonary ends then were oversewn with interrupted OOOOO silk, and a pledget of Gelfoam was left between the ends. The lung was reinflated, and the incisions were closed as usual.

DR. SCHMUTZLER: After operation, the child did reasonably well for some hours; her condition then deteriorated, and she died on the day after operation.

DR. EDWARDS: Necropsy disclosed that the right pulmonary artery did not arise from the pulmonary trunk but from the aorta. A surgically divided, left-sided, patent ductus arteriosus was present (Fig. 3).

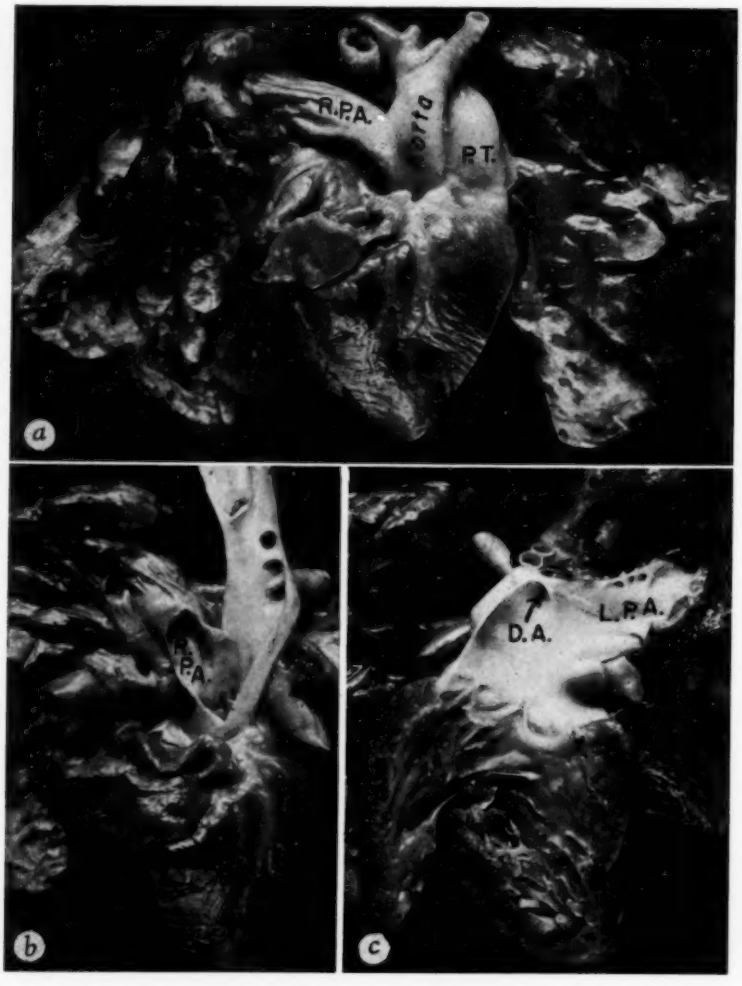

Fig. 4.—*a*, The heart, lungs, and great vessels viewed from the front. The right pulmonary artery (*R.P.A.*), which on further dissection was found to originate from the aorta, lies in an essentially normal position. From the exterior, it is not possible to be certain whether the artery takes origin from the aorta or whether it pursues a normal course behind the aorta to join the pulmonary trunk (*P.T.*). *b*, The aorta (*A.*) has been opened along its right aspect, and the right pulmonary artery has been opened in front, showing the origin of the latter from the ascending aorta. A zone of stenosis was not present in the anomalously arising right pulmonary artery. *c*, The right ventricle and pulmonary trunk. The left pulmonary artery (*L.P.A.*) arises as a continuation of the pulmonary trunk. The site of the ductus arteriosus (*D.A.*), which has been divided surgically, is also shown. Of significance is the fact that a right pulmonary arterial branch was not present in the pulmonary trunk.

From external examination of the necropsy specimen, the right pulmonary artery appeared to pursue a normal course. Its relationship with the aorta could not definitely be determined as abnormal. It was possible that the vessel either arose from the ascending aorta or passed in a normal manner behind the ascending aorta to take origin from the pulmonary trunk (Fig. 4,*a*). The right pulmonary artery uniformly measured about 1 cm. in diameter.

After the specimen was opened, it became apparent that the right pulmonary artery did arise from the right side of the ascending aorta (Fig. 4,*b*). The pulmonary trunk arose normally from the right ventricle and had a normal relationship with the ascending aorta. An ostium of the right pulmonary artery was not present. The pulmonary trunk simply continued as the left pulmonary artery (Fig. 4,*c*). The ostium of the ductus arteriosus, which had been closed surgically, was at the usual location of the ductus arteriosus. The aortic insertion of the ductus arteriosus was into the aortic arch, which was on the left, the point of insertion being just beyond the left subclavian artery. Both the systemic and pulmonary venous connections with the heart were normal (Fig. 5).

The left atrium and left ventricle were dilated, with mild epicardial thickening in both chambers, particularly the atrium.

The developmental basis for origin of the right pulmonary artery from the ascending aorta may depend on abnormalities in the sixth right aortic arch. It will be recalled that each pulmonary artery arises as a branch of its corresponding sixth aortic arch. On the left side, the distal end of the sixth arch persists as the ductus arteriosus, whereas on the right side, the distal end of the sixth aortic arch normally disappears, leaving only the proximal part of the sixth arch as the origin of the right pulmonary artery, and the remainder of the right pulmonary artery is the afore-mentioned branch of the right sixth arch.

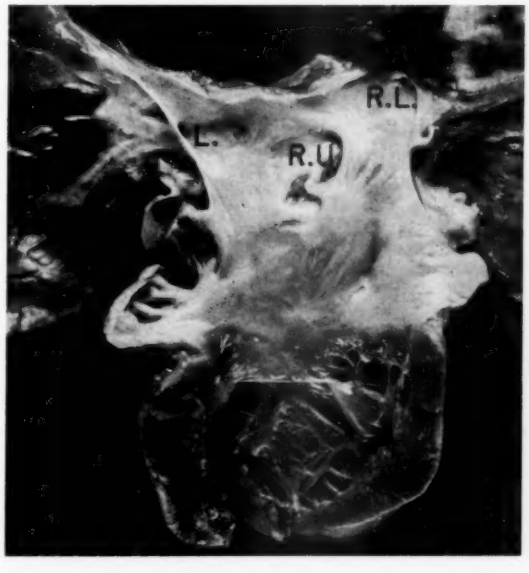

Fig. 5.—Left side of heart, showing normal connection of pulmonary veins with left atrium. *L.*, Confluence of left upper and left lower pulmonary veins. *R.L.*, Right lower pulmonary vein. *R.U.*, Right upper pulmonary vein.

In the malformation in this case, it is possible that, instead of the distal end of the right sixth aortic arch disappearing, the process of resorption had occurred in the proximal part of the right sixth arch, whereas the distal portion remained patent and connected with the aorta. In this way, the proximal part of the anomalously arising pulmonary artery may be viewed as the distal persisting part of the right sixth aortic arch.

DR. SCHMUTZLER: Dr. DuShane, would you comment on the possibility of making this diagnosis in the future, fortified with the experience in this case?

DR. DUSHANE: I think that the only chance of making this diagnosis before operation rests in the laboratory. Dr. Swan, would you care to comment about the advantages of angiocardiography in such a case?

DR. SWAN: The techniques used in the laboratory study of this infant were inadequate to allow complete evaluation. We had noticed, of course, that it was not possible to pass a catheter into the right pulmonary artery, and only with difficulty could it be made to enter the left. I am fairly certain that technically satisfactory angiocardiography would have given the complete diagnosis in this case. A selective injection made into the right ventricle would have demonstrated the absence of the right pulmonary artery and the presence of the left pulmonary artery. In an infant of this size, despite dilution of the contrast medium because of the left-to-right shunt, visualization of the anomalously arising right pulmonary artery and of the patent ductus arteriosus would have been possible when the medium reached the aorta.

DR. EDWARDS: Dr. Kirklin, you will recall from the pathologic description that, except for its abnormal origin, the course of the right pulmonary artery was normal. Also, the origin of the artery from the aorta was near the pulmonary trunk. Could you discuss the possibilities of surgical correction in such a case?

DR. KIRKLIN: In regard to the possibility of surgical correction of anomalous origin of the right pulmonary artery from the aorta in association with a patent ductus arteriosus, the diagnosis certainly would have to be made preoperatively. Through a left thoracotomy incision, it is unlikely that one could identify this added abnormality of the right pulmonary artery.

A categoric statement cannot be made concerning the possibility of complete correction of this malformation. It is always hazardous to theorize as to what might be possible in the future. It would appear, however, that such a procedure might be extremely difficult without the use of a graft. One would have great hesitancy in using a graft in the pulmonary artery, particularly in a small child, because of the great probability of technical failure. I know of at least one unreported patient, operated upon by a surgeon in another institution, in whom the ductus was closed and the right pulmonary artery was ligated. This infant has done well in the early postoperative period, but, of course, no one knows the future of a child with only one functioning pulmonary artery. One might suspect, however, that the child would have a reasonably good outlook.

Diagnosis: Origin of Right Pulmonary Artery From Descending Aorta

Annotations

Value of the Q-T Interval

The Q-T interval is the electrocardiographic representation of electrical systole in the ventricle (beginning with isometric contraction and ending with onset of isometric relaxation). The interval is measured in the standard leads and begins at the first deflection of the QRS and extends to the end of the T wave. (When a U wave or P wave is superimposed, accurate measurement is almost impossible.) The length varies with cardiac rate, and for this reason, a formula correcting the Q-T interval according to cardiac rate is utilized ($Q\text{-}T_c = \frac{Q\text{-}T}{R\text{-}R}$). The $Q\text{-}T_c$ should not exceed 0.405 second.*[1]

Although the Q-T interval is of little value in providing information about organic or structural cardiac abnormalities, it is of distinct value in the recognition of various abnormal electrolyte states, i.e., hyper- and hypocalcemia, hyper- and hypokalemia, alkalosis and acidosis, and in quinidine therapy. The effect of these extracellular alterations is upon the transmembrane potential of the myocardial syncytium.[2] The number of factors which modify the transmembrane potential can hardly be limited to the six electrolyte states mentioned above, but to the present time these are the most frequently recognized clinical situations in which the Q-T interval may be of clinical value if carefully observed.

The changes seen with high and low levels of serum potassium are well known, and other than to reiterate that these changes involve primarily the T wave in prolonging or shortening the S-T segment, hyper- and hypokalemia will not be discussed.

In hypercalcemia, due to any of its many causes, there is a shortening of electrical systole (Q-T interval). The membrane resting potential (MRP) is decreased. The initial stages of repolarization are greatly accelerated, the plateau characteristic being lost.[2] In the electrocardiogram the shortening is within the S-T segment, whereas the T wave is undisturbed, so that gross abnormality of complexes is not apparent, and only by careful measurement will the shortened or prolonged interval be detected.

Conversely, in hypocalcemia the Q-T is prolonged because of an extension of the S-T segment. The plateau phase (of electrical recovery) is increased.[2]

Yu[3] plotted S-T segments and $Q\text{-}T_c$ intervals against levels of serum calcium in 34 patients having either hyper- or hypocalcemia and noted the coefficient of correlation to be highly significant. The length of the S-T segment and that of the $Q\text{-}T_c$ interval were inversely related to the level of serum calcium.

Acidosis and alkalosis usually represent a combination of electrolyte derangements simultaneously. In acidosis, the ECG pattern usually resembles that of hyperkalemia, with a tall, shortened T wave. In alkalosis, the pattern is somewhat variable, depending on the underlying cause. Respiratory alkalosis secondary to hyperventilation will cause the pattern of hypocalcemia, whereas metabolic alkalosis may appear as either a low, widened T wave or a prolonged S-T segment, or as both. Quinidine will cause flattening and widening of the T wave.

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*Upper limit of normal according to New York Heart Association criteria is 0.425 sec.[4] Yu[3] (Rochester), 0.43 and 0.36 sec. Ashman and Hull[5] 0.44 and 0.35 sec.

These are the major causes of an abnormal Q-T interval which occur frequently in clinical situations. The less common causes have been left for a more esoteric discussion.

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The Electrocardiogram in the "Tear Drop" Heart

The electrocardiogram in the patient with a thin, elongated thorax and a narrow vertical heart often presents patterns which might be considered abnormal if these clinical features are not recognized. A delayed R′ in Leads V_1 and V_2 suggests right bundle branch block or other aberrant depolarization. A deep Q wave in Leads V_4, V_5, or V_6 might be mistaken as indicating lateral wall infarction.

These patterns are explained when one realizes that the positioning of the electrode on the chest wall is standardized according to the average thoracic shape and cardiac contour. However, in the patient who is tall and thin, and who also has a "tear drop"-shaped heart, the relationship

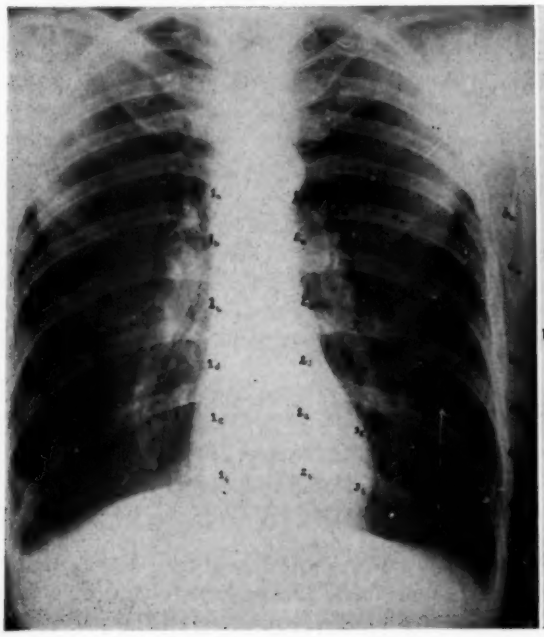

Fig. 1.

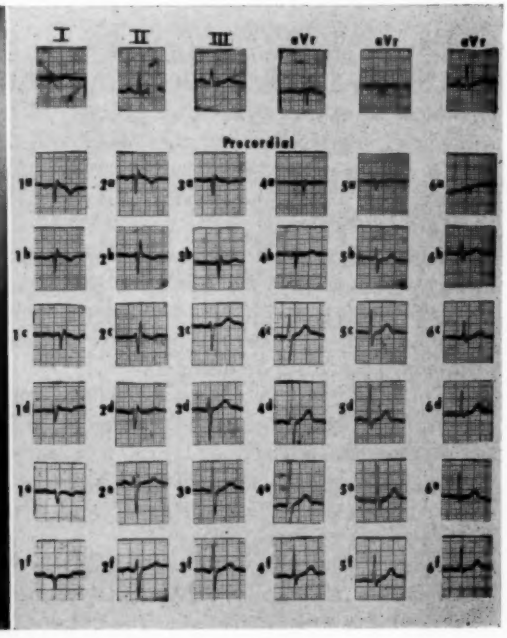

Fig. 2.

Fig. 1.—A "tear drop"-shaped heart in an elongated thorax. The numbers *1c—6c* correspond to the standard placement of the exploring electrode on the precordium.

Fig. 2.—The electrocardiogram of the patient whose x-ray is seen in Fig. 1. The precordial lead complexes correspond to those superimposed upon the x-ray.

of his heart to the fourth intercostal space is considerably lower than the average (Fig. 1). The equivalent recording of Leads V_1 and V_2 in this patient may be in the fifth or even sixth intercostal spaces (Fig. 2). The R′ recorded in the standard positions for Leads V_1 and V_2 represents normal depolarization of the posterior basal segment of the heart. This can be confirmed by simultaneous esophageal lead tracing.

Similarly, a Q wave in Leads V_4, V_5, or V_6 in the standard positions, or slightly above, does not necessarily indicate lateral wall myocardial infarction, but more likely is recording the potential from within the left ventricle and should be regarded as a normal complex.

If these patterns present without concomitant evidence of right bundle branch block or myocardial infarction, investigation of the physical features may enable more accurate interpretation.

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Ballistocardiography as a Result of Cooperation Between Sciences

The early investigators in the field now known as ballistocardiography, who conducted their studies in various European and American cities without, for the most part, any knowledge of each other's work, devised methods and made observations which were so diverse that it would be difficult to put together the information secured. The aim of these investigators was to obtain physiological and clinical information about the human circulation with the aid of physical methods and recording apparatus; however, the obstacles they encountered were great and, to some extent, of a new kind. Their research may be considered an extension of that done in the old European schools by physiologists and clinicians who, with some success, tackled problems such as the determination of stroke volume and the clarification of pulse wave transmission.

The study of the biophysics of the human circulation, now approached from another angle and by different means, began to attract general attention after the physiologist-clinician Starr was able to show how much the ballistocardiogram depends on the state of cardiac and vascular performance. Starr's own interest had been aroused by Yandell Henderson, also a physiologist. Once again, general attention was focused on a biophysical problem by the medical profession, although some of the early students of ballistocardiography were of different backgrounds altogether; among them was a geophysicist, and Gordon, one of the founders, does not seem to have been a physician either. At this time, physicists (among others Burger and Talbot) became intrigued by these problems, formulated them properly, and initiated in the field the systematic application of physics, and, making use of the developments in instrumentation, bridged some of the gaps the old schools had to deal with. It gradually became clear that neither the physicians nor the physicists could independently solve problems such as those concerned in ballistocardiography, and an intensive cooperation got under way.

When Starr first began his work in ballistocardiography, he used Henderson's (and Gordon's) bed of ultralow natural frequency (ULF) and recorded its displacement, but, in order to avoid the necessity of having the subjects and patients hold the breath—a procedure that some patients find impossible, that some perform differently than others, and that is well known to affect appreciably the abnormal circulation—he soon designed his high-frequency (HF) table, again recording displacement. Some years later, Dock introduced his direct-body technique, which proved to be simple enough for immediate clinical application insofar as the handling of the instrument was concerned.

Starting out from Newton's laws, the physicists could interpret quantitatively why these three types of ballistocardiographs give different results on the same person. First, because of the difference in mechanical properties of the ULF and HF instruments, different aspects of the circulatory events, namely, displacement and acceleration of the center of gravity inside the body, are represented quantitatively by the displacement tracings. Second, the motion of the subject on his own tissue layer, on which the Dock ballistocardiogram is based, affects records secured from the HF instrument, and slightly affects those from the ULF instrument as well. This evaluation of two mass systems indicated that the ULF instrument gives the smallest distortion, and that by recording its acceleration a force ballistocardiogram can be obtained just as free of respira-

tory effects as that from the HF instrument. Other results are that ballistocardiograms secured from different types of instruments can be transformed into each other, and the clarification of why a striking resonance is visible in direct-body tracings.

However, some of the complications affecting the high-frequency components of ballistocardiograms need additional clarification, such as the transmission from the cardiovascular system to the body frame, the movement of body parts relative to one another, and the movement of tissue caused by the changing volume of the heart and of the blood vessels. The available evidence suggests that these effects are of minor importance for the longitudinal components of the movement, that is, only insofar as notches and slurs are concerned.

The development of lightweight ULF ballistocardiographs, with up to six degrees of freedom, made possible animal experiments on a ballistocardiograph. Such experiments had up to that time been very crude, although focusing attention once more on a basic problem: the interpretation of the record. Starr and Hamilton and associates had already been able to calculate the force ballistocardiogram, starting out from ejection curves. These approximations provided strong evidence for the theory that the greater part of the ballistocardiogram is originated by movement of blood in the large vessels. Cossio, however, concluded from animal experiments in which he occluded both inflow and outflow of the heart that most of the curve is due to movement of the heart inside the body. More recent experiments on dogs (Scarborough and Honig), carried out on ULF ballistocardiographs, did not support Cossio's view. They do suggest, however, that motion of the heart contributes appreciably to the ballistocardiogram. This conclusion was also reached by Burger and Noordergraaf in their calculation of the normal ULF displacement, velocity, and acceleration ballistocardiogram from the changing distribution of blood in the large and small arteries and in the heart, and the latter's motion as derived from other information concerning the heart's behavior. This calculation, which includes several assumptions that have to be checked, results in predicted curves closely resembling the average normal experimental ballistocardiograms.

The quantitative evaluation of the effects of aging, tortuosity, and of an abnormally performing circulatory system has scarcely been started.

Attempts to interpret the ballistocardiogram have greatly stimulated the search for methods to measure not only local pulsatile blood flow itself, but also the elastic properties of blood vessels in vivo. New methods for continuous determination of the ejection curve (the "force of the heart") and thus of the stroke volume, and of the latter directly are being developed, while characteristics of the records of use in recognizing definite clinical abnormalities are emerging gradually. All this could result because of the unity of method attained through a straightforward formulation of the underlying problems.

One can hardly imagine that the growth in, and dissemination of, understanding of circulatory phenomena could have evolved so rapidly without this cooperation, the scope of which is fortunately still widening and deepening.

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Essential Hypertension

In 1954, Hamilton, Pickering, Fraser Roberts and Sowry[1] published their study of the frequency distribution of blood pressure in the general population. For each age-group they obtained a single curve, Gaussian or skewed; there was no evidence that any one of the age-groups contained two populations, one with "normal" pressure and one with "hypertension." Again, when they studied the relatives of those subjects who (by conventional criteria) had hypertension, the curves were not bimodal. The authors concluded that "hypertension" may consist merely of the upper end of a continuous distribution, and that no exact demarcation between normal and high blood pressure exists.

This important study had considerable bearing upon the conventional concept of essential hypertension as "a disease," and it seemed that this concept might have to be rejected. Sir Robert

Platt, himself a proponent of the hypothesis that essential hypertension is an entity which is inherited by Mendelian dominance, has now re-examined the data of Pickering and his colleagues. Sir Robert selected siblings aged 45 to 60 of "hypertensives" aged 45 to 60, intending in this way to exclude from both groups, as far as possible, the confounding factors of secondary hypertension and senile hypertension. The frequency distribution among the siblings had a bimodal form for both systolic and diastolic pressures. The main dip in the curves corresponded to a pressure of 150/90 mm. Hg, which is exactly the conventional clinical dividing line between normal and high blood pressure in middle age. Therefore, Sir Robert considers that the data do not warrant a conclusion at variance with conventional views.

The position now is therefore stalemated. In order to force a decision on this extremely intricate battlefront, the game will have to be played again with many more pieces on the board. Sir Robert is no doubt right in his view that the pieces do not yet exist and that "a prospective survey lasting at least twenty years" will be necessary to produce them. But will the manufacturers and prescribers of hypotensive drugs be content to wait?

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Aphorisms

In the nineteenth century, a small volume was published by Napoleon's physician, Baron Corvisart, called *Aphorisms*. This consisted of philosophical comments on medicine, as well as clinical wisdom distilled from bedside observations. Many of these aphorisms were collected by his pupils and were finally published under his name. On reading them today, one finds that the philosophical comments appear pompous, airy, and sometimes downright silly. Some of the observations on clinical medicine are simply incorrect, whereas others are shrewd, informed, and relevant today. Despite this mixture of effects, the volume has the value of being representative historically of the bedside medical thinking of that day. Through such a book, we can feel the medical climate of nineteenth century France, and see the direction that medicine was eventually to take.

The perspective of the years has determined the relative valuelessness, except in a historical sense, of the windy philosophy and the lofty conclusions based upon inadequate evidence of most of the comments found in this book, but insofar as the direct clinical observations themselves are concerned, and the reasoned comments based upon these observations, the years have, if anything, enhanced and high-lighted their value. Perhaps our own milieu of bedside clinical medicine, which often contains the raw material for research, should be more carefully documented than it is.

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The Taxicab as an Aid in the Economic Rehabilitation of Patients With Advanced Heart Disease

There are many cardiac patients with advanced but fairly stable or only slowly progressive heart disease, who might lead happier and more useful lives if they could retain their jobs. Patients with severe cardiac disabilities are generally told by their physicians to quit work entirely and permanently. I refer to grade-three or grade-four cardiac patients. These include patients with angina who have spells of pain at rest or when walking a half block in the street, or who consume

ten or more nitroglycerin pills daily, but who feel quite well at other times. They often have little pain when indoors and can carry on quite a bit of activity, except out of doors. Another group comprises those cardiac patients who have irreversible congestive heart failure from chronic rheumatic valvular disease, or, less often, from hypertension or coronary artery disease. These patients may have an enlarged, congested liver, and a tendency to swelling of the legs and abdomen, and râles in the lungs, with or without hydrothorax. They generally are on a full course of treatment for heart failure, i.e., low-salt diet, digitalis, oral diuretics, and periodic injections of mercury, or paracentesis.

When confronted with such an apparently grave situation, the physician at first may hope to establish cardiac compensation by his treatment. If he fails or finds that congestive symptoms and signs quickly return after an initial success, he is prone to regard the condition so seriously that he prohibits the patient from returning to work. In many instances the employer discharges the worker, even if the latter wishes and seems able to return to work (numerous injustices in the employment of cardiac patients still prevail). In other cases, the type of employment is entirely unsuitable or too difficult for the patient with advanced heart disease. There are many patients, however, whose jobs are still available, and who could readily do the work satisfactorily, but who cannot travel back and forth to work. They cannot walk the necessary distance to the streetcar or climb the stairs in the subway or to reach the elevated trains. They cannot buck the cold winds or storms of winter. If the matter of transportation were solved, they would have no difficulty at all with the actual indoor work which they have been doing for years. Such patients should be urged to spend ten to fifteen dollars a week on taxi fares if necessary. They would then have to take no more than a few steps to go from the front door of their homes to the taxi, and then a few more steps from the taxi to their place of employment. This investment might enable a man or woman to earn seventy-five to one hundred dollars a week, and the net remainder from the weekly wage would help keep the wolf from the door. The expense of transportation might even be decreased if pools could be arranged so that several handicapped individuals could ride to town together. To people in humble circumstances this simple advice might enable the father of a family to support his children for some years while they were growing up. Then, when the children had reached the age of self-support, they would be able to take over some of the financial responsibilities. Instead of becoming a public charge, such an individual would retain his self-respect, keep in a better mental state, and lead a happier and more worth-while life.

Generally, the physician fears to let such a patient go to work. It is regarded as contrary to general practice to permit a patient with advanced heart disease to work. The physician may fear that if anything happens to the patient, he will be blamed. Or he may think that doing some kind of light work will shorten the patient's life. As to the latter, it is very doubtful whether doing indoor secretarial or light sedentary work shortens a cardiac patient's life. Even if the length of life is shortened by a few months, most of the individuals in this group would much prefer to live a self-respecting life for a few years than a slightly longer one as a public charge or dependent on other members of the family. I believe that, apart from these patients with very much advanced heart disease, physicians have been too prone to restrict patients with moderately well-compensated cardiac lesions. Such patients often will find it difficult or impossible to obtain a new position if they leave their old and accustomed job. The physician should weigh the sociological and domestic factors most carefully before giving advice that will unnecessarily destroy or jeopardize the patient's earning power.

In a word, the investment in taxicab transportation may be the one method of economic rehabilitation in patients with advanced heart disease. It may enable some of these extremely handicapped individuals to live a self-supporting and self-respecting life instead of being a charge on others.

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Letter to the Editor

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JANUARY 15, 1960

Re: Cardiac Muscle Tone

To the Editor:

In analyzing pressure tracings during catheter studies of outflow obstructive lesions, e.g., aortic and pulmonary stenoses, we observed that a raised diastolic pressure was found, respectively, in the left and right ventricles in cases particularly in which obvious hypertrophy was reflected in the electrocardiogram. It would appear that this raised diastolic pressure could best be explained by an increase in cardiac muscle tone. Various signs in cardiac function could be related to this basic reaction, and, if accepted, these could indicate the best policy in the management of at least left ventricular failure.

Measurements in a 26-year-old patient with pulmonary valvular stenosis are representative. In such a case the outflow resistance would be a constant, so that rapid changes in intraventricular pressures induced by pharmacologic means must be related to filling pressures and to muscular tone. A slow drip infusion of 10 mg. of morphine was first given and followed for ¾ hour; no apparent effects were measurable. Thereafter another 10 mg. was injected directly into the catheter. Maximal changes were registered 30 minutes later when the right ventricular systolic pressure rose from a mean 100 mm. Hg to 160 mm. Hg, and the mean diastolic pressure of 12 mm. Hg dropped to nil. With outflow obstruction constant, the raised systolic pressure could be achieved, partly by lowered resistance to the atrial filling pressure, i.e., reduced ventricular muscle tone allowing an increase in ventricular volume during the filling phase.

A similar observation was achieved with theophylline ethylenediamine in another patient with pulmonary stenosis. Intravenous administration of 250 mg. stepped up the mean systolic pressure (right ventricle) from 90 to 115 mm. Hg after 7 minutes; diastolic pressure dropped from 7 to 5 mm. Hg over this short period. Clinical experience reveals that the cyanotic syncope of the trilogy of Fallot is alleviated by the use of morphine. According to our postulate, this could be due to a relaxation of diastolic tone resulting in increased right ventricular diastolic volume and systolic pressure and increased pulmonary blood flow.

The beneficial effects of morphine and of theophylline ethylenediamine, particularly in left ventricular failure, have often been demonstrated in clinical practice; no adequate explanation for these effects has as yet been forthcoming. At least part thereof could be explained by the myotropic effect with reduction in diastolic tone.

The increased diastolic tone present could be explained as a protective mechanism preventing the overdistention of muscle fibers by an overlarge diastolic volume and obviating a too high systolic pressure in conjunction therewith. As an attempt to keep the muscle fiber within the critical hump of the Starling curve, it would protect the reserve of adequately functioning fibers.

It is conceived that cardiac tone is probably controlled and interrelated between the chambers by a neurogenic reflex mechanism initiated from stretch receptors, through the autonomic nervous system.

The following diagnostic features can be related to this basic finding:

1. Increase in diastolic tone of the *left ventricle* would necessitate an increased left atrial filling pressure, eventually increased pulmonary venous pressure, and, ultimately, pulmonary edema. Therefore, the findings of raised pressure in and distention of the pulmonary venous system and of the left atrium (ECG and roentgen film) would be a rough diagnostic indication of the pressure situation (a) in acute cases with a discrepancy between the normal output and the actual output, and (b) in more chronic cases with a varying residual volume in the pulmonary venous system; this would vary with the diastolic tone in the left ventricle and be manifested clinically as a variable dyspnea. Such findings, enlarged left atrium and pulmonary venous system, would be of diagnostic and prognostic significance, e.g., in hypertension. A gallop rhythm, due to what is taken to be an accentuated third heart sound, could in such cases indicate an increased resistance impact during left ventricular filling due to increased left ventricular tone. The presystolic or atrial gallop would indicate that the left atrium has become a high-pressure pump chamber.

2. Increased tone in the *right ventricle* would have similar effects on the right atrium and the systemic venous system. The accentuated *a* wave in jugular tracings, e.g., in pulmonary hypertension, could be regarded as an indication of the tonic resistance of the right ventricular muscle to the filling pressure of the right atrium. In cases of aortic stenosis, similar *a* waves may be explained by a reciprocal increase in tone of the right ventricle following an increase in tone in the left ventricle and raised left atrial systolic pressure. The increased venous pressure again could indicate in acute cases the discrepancy between the expected and the actual output of the right ventricle. The vast possibilities by volume adaptation in the inferior vena caval system could explain the rarity of a gallop of right ventricular origin.

If this postulate based on diastolic tone is confirmed, the basic principles in the management of left ventricular failure and of myocardial infarction may be viewed from a different angle. By adjusting the diastolic volume and therefore the total work, the process of left ventricular failure can be seen as a "protective" mechanism against overload. The nice and adaptive balance between normal output of right and of left ventricles is probably achieved by the neurogenic reflex mechanism. If morphine were to act on the right ventricle alone, the increase in output would mechanically overwhelm a weakened left ventricle, which would fail more readily. By its action however on the left ventricle also, the release in local tone brings about a rapid decrease in pulmonary venous pressure and edema, with, at times, dramatic relief of symptoms. It can be conceived that in myocardial infarction the muscle fibers develop a marked increase in tone, as happens in the event of injury in any part of the arterial system. The increase in left ventricular tone could result in lowered output, raised left atrial pressure, and pulmonary congestion with edema. Noradrenaline increases the tone of the cardiac muscle and could aggravate these results.

Failing cardiac muscle can best be served pharmacologically by improving the inotropic function (the most beneficial effect of digitalis and Strophanthus glycosides, electrolytes, etc.), combined with a damping of the rising diastolic tone (morphine, theophylline ethylenediamine). In the face of an overburdened or weakened muscle the latter have a very temporary value.

Further pressure analyses of suitable cases are needed to confirm this suggested sequence of events.

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Book Reviews

LA RAUWOLFIA: CHIMICA, FARMACOLOGIA ED APPLICAZIONI CLINICHE. By L. Meciani, Milano, Italy, 1957, Casa Editrice Ambrosiana, 582 pages.

This work probably represents the most complete exposition on Rauwolfia serpentina and its derivatives available at the present time. The volume includes many illustrations, tables, and charts. The chemistry of rauwolfia is completely discussed, the pharmacological action of the drug outlined, and its clinical applications reviewed. In addition to being an exhaustive analysis of the drug and its allied derivatives, this book is an excellent source for reference material, there being 1,850 references cited in the bibliography.

CINEFLUOROGRAPHY. Edited by George H. S. Ramsey, M.D., Professor and Chairman, Department of Radiology; James S. Watson, Jr., M.D., Research Professor, Department of Radiology; Theodore A. Tristan, M.D., Senior Instructor, Department of Radiology; Sydney Weinberg, Research Associate, Department of Radiology; and William S. Cornwell, M.A., Clinical Associate, Department of Radiology, University of Rochester School of Medicine and Dentistry, Rochester, N. Y. Springfield, Ill., 1959, Charles C Thomas, Publisher, 266 pages. Price $11.75.

This book summarizes the Proceedings of the First Annual Symposium on Cinefluorography, sponsored by the Department of Radiology of the University of Rochester School of Medicine and Dentistry, November 14 and 15, 1958. Seventeen short presentations dealing with different technical aspects of instrumentation for cinefluorography are included. These range from general discussions of the principles of image intensification and solid-state amplifying screens to specific descriptions of four separate image intensifiers. Editing and format are excellent. A bibliography is provided. This volume will be of value to those concerned with the engineering aspects of this very promising field.

ACUTE PERICARDITIS. By David H. Spodick, M.D., Senior Physician and Chief, Cardiographic Laboratory of the Medical Services, Lemuel Shattuck Hospital; Clinical Survey Director, Department of Cardiology, The Boston Evening Clinic; Associate Fellow of the American College of Cardiology; Clinical Instructor in Medicine, Tufts University School of Medicine. New York, 1959, Grune & Stratton, Inc., 175 pages, 28 illustrations. Price $6.50.

In the preface, Dr. Spodick writes, "My intention has been to present acute pericarditis from the viewpoint of the clinician but with considerable emphasis upon basic concepts and their application to diagnosis and management." Within this scope, the author has done an admirable job. The information provided is unusually complete for a volume of such small size. Discussions cover not only the older, well-known forms of pericarditis, but also the rarer forms and the more recently recognized states, including the postcommissurotomy syndrome and postmyocardial infarction syndrome. Recently recommended techniques, such as electrocardiographic needle guidance during pericardial paracentesis and diagnostic intravascular carbon-dioxide negative

contrast roentgenography, are discussed briefly. For what is not covered extensively enough in the text, the reader is provided with a ready source of over 400 selected references. From the strictly clinical standpoint, deficiencies in the text are few. Because of the frequency with which it is used, perhaps more should be included concerning the subtleties of electrocardiographic monitoring during pericardial paracentesis. The little-known but frequently valuable contribution of fluoroscopic observations of the right atrial pulsations, in the diagnosis of pericardial effusion, is neglected.

For the general internist, this monograph provides a significant amount of important data on pericarditis which has not been stressed adequately in the medical literature. Even the cardiologist may be surprised at what he can gain from the collection of information in this small book.

LE COEUR (Tome II). By Camille Lian et ses Eleves, Paris, 1959, L'Expansion Editeur, 278 pages, 19 illustrations. Price: 2,000 francs.

This book constitutes the second part of a series of three, following the first which dealt with: Exploration du coeur et grands syndromes cardiaques (p. 320).

This second part is divided into two subdivisions: (1) organic diseases of the heart (pericardial and endocardial affections, chronic valvulopathies, myocardial syndromes, and congenital cardiac malformations); and (2) involvement of the heart in primarily noncardiac diseases (nutritional states, neuroses, infections, intoxications, parasitoses, respiratory conditions, renal and digestive diseases, syphilis, hemopathias, traumas, tumors).

The book aims to guide the practitioner "onto the way to diagnosis," and then to inform him of the prognosis and provide him with treatment "with all necessary details." So vast an ambition hardly could blossom in so short a work, that, rather, is a "primary" of practical cardiology. Nonetheless, the scheme is clear and rational. The clinical semiological study is generally good, and the auscultation data are accurately backed by phonocardiographic information, in which the senior author's own experience overtly appears. Conversely, the other fundamental complementary methods of investigation (electrocardiography, left and even conventional right heart catheterization, modern and various methods of determination of shunts, angiocardiography) are but superficially referred to, if not omitted.

As to the considerations of heart surgery, they often appear to be outdated (methods and indications), obviously because of the fast changes in that field.

Regarding other sections, more specific comments may be made. Omissions and highly questionable statements are to be pointed out. Concerning rheumatic endocarditis, throat cultures have not been mentioned, and the prime interest of high antibody titers (especially A.S.O.) in dubious cases has not been stressed—being given the same rank as leukocytosis. Corticotherapy of rheumatic carditis has been advised for 2 to 3 weeks—a very short while indeed. Streptococcal prophylaxis by oral penicillin has been limited to 10 days a month (?) for 5 years, in association with the administration of aspirin—an unusual method.

The natural history of mitral stenosis is not clear. Mechanical disturbances ascribable to to mitral blockade have been incorporated within the framework of (congestive) heart failure—which is quite misleading. Anticoagulant therapy is routinely advised for 2 to 3 weeks before any attempt is made to reverse atrial fibrillation—a very controversial opinion. Ligation of the inferior vena cava is advocated in cases "when (mitral) commissurotomy is turned down by the (patient's) family." Subtotal thyroidectomy is strongly advised in hyperthyroid mitral patients (p. 90), while elsewhere (p. 174) one reads that I^{131} is to be considered as the adequate, modern treatment of thyrotoxicosis in place of surgery.

The concept of Eisenmenger complex is obsolete, since the reader might thus consider it as an autonomous anatomic entity.

The authors' pathophysiologic concept of chronic cor pulmonale is strange. Apparently, they deny to generalized obstructive emphysema that prominent role which has been universally recognized, incriminating in contrast a "functional thoracic distention" from skeletal and bronchial origin. Furthermore, they do not pay any attention to the second, and quite different, mechanism occasionally responsible for chronic cor pulmonale, i.e., alveolo-capillar block that interferes with

gas-exchanges in interstitial fibroses from various causes. They mention the role of anoxia but not that of hypercapnia. Treatment of chronic cor pulmonale is very superficially covered, causing a general feeling of confusion to ensue in the reader. The section dealing with the heart in obesity does not mention the possible evolution to chronic cor pulmonale.

Two chapters are excellent: the clear and concise one devoted to miscellaneous myocardial involvements (of known and unknown origin—idiopathic hypertrophy), and the chapter dealing with cardiac neuroses.

The printing is good. The references, in limited number and almost exclusively French (75 out of 88), provide the reader with a fair appreciation of the senior author's interest in cardiovascular investigation back to 1913.

On the whole, despite the foregoing criticisms, this book is of interest and might prove really useful to French-speaking general practitioners and senior medical students.

ATLAS INTRACARDIALER DRUCKKURVEN (Atlas of Intracardiac Pressure Curves) (Atlas de Curvas Tensionales Intracardias). By Prof. Dr. Otto Bayer and Dr. Hans Helmut Wolter. English translation by Dr. G. R. Graham, London. Spanish translation by Dr. E. Low-Maus, Barcelona. Introduction by Prof. Dr. Andre Cournand, Columbia University, New York. Stuttgart, 1959, Georg Thieme Verlag, 185 pages, 97 illustrations. U. S. and Canadian agents: Intercontinental Medical Book Corporation, New York, N. Y. Price $16.20.

This atlas presents a series of pressure records which the authors have collected during right heart catheterization by means of a capacitance manometer system. A general section contains a brief theoretical chapter followed by a description of the pressure phenomena under normal and abnormal circumstances. A short chapter discussing technical pitfalls, distortions, and artefacts leads into the atlas section proper, which consists of a series of illustrations of abnormal pressures.

It is always interesting to look at somebody's records, and for this reason the atlas will find its way into cardiovascular laboratories as a supplementary teaching aid. However, beyond this the book offers little to the clinical physiologist. If written with the intent of introducing the beginner to hemodynamic techniques obtainable in human subjects, the lack of a thorough discussion of the technical and physiologic background constitutes a drawback. No mention is made of the uses of endocardial electrocardiography and phonocardiography, which omission is perhaps not serious. However, the exclusion of left-sided pressure phenomena and the absence of a discussion of the aortic (central) pulse contour is regrettable, since many day-by-day decisions in medical and surgical cardiology depend on such data and on their interrelationship to right-sided events. For the same reason, the omission of flow data will make any discussion of pressure records incomplete. These shortcomings are all the more apparent since the material is otherwise well presented and carefully edited.

ARTERIAL EMBOLISM IN THE LIMBS. By A. L. Jacobs, M.A., D.M. (Oxon.), F.R.C.P., Physician to the Whittington Hospital, London, England. Edinburgh and London, 1959, E. & S. Livingstone, Ltd., 200 pages, 37 illustrations. U. S. agents: Williams & Wilkins Co., Baltimore, Md. Price $8.00.

In this book, A. L. Jacobs has analyzed his experiences with 69 patients observed during acute peripheral arterial embolization over a period of 16 years in three general hospitals in London. It is one of several monographs on this subject which have appeared in recent years.

The approach is primarily clinical, and the background is largely anatomical. The clinical observations are remarkably detailed and of excellent quality. Numerous charts and diagrams clarify the analysis of the data. The importance of collateral circulation in determining limb survival is emphasized, and is supported by radiography of postmortem specimens after arterial injection of radiopaque fluid.

The major weakness of the book is in the physiologic sphere. The author is highly critical of all physiologic experiments purporting to prove the existence of associated arteriospasm, but presents no physiologic data of his own. He attributes arterial narrowing, for example, to the adaptation of the artery to decreased flow, but does not consider this to represent abnormal constriction. He also makes little distinction between the function of small and large arteries and does not seem to realize that vasoconstriction of the one group may be associated with vasodilatation of the other, or that vasodilatation can follow vasoconstriction temporally. In an effort to confine his discussion to peripheral arterial embolism only, he has ignored a great deal of pertinent physiologic and pathologic data from the literature.

In contrast to his critical attitude toward physiologic experiments, however, he tends to explain away objections to interpretations based on his own radiographic injection data, such as interference from postmortem clots, etc. He also discusses the difficulties in diagnosis of arterial embolism but does not face squarely the possibility that some of the cases he presents as embolism may in reality be in situ thrombosis.

Despite this bias, which is after all only human, the book is a serious and very well-written critical analysis of the subject of peripheral arterial embolism and is recommended for inclusion in the libraries of all those interested in cardiovascular diseases.

ANGIOLOGIE. PATHOLOGIE, KLINIK UND THERAPIE DER PERIPHEREN DURCHBLUTUNGSSTÖRUNGEN. Edited by Prof. Dr. Max Ratschow, F.A.C.A., Ehem. Direktor der II. Med. Univ.-Klinik Halle-Wittenberg, jetzt der Med. Klinik Darmstadt, Vizepräsident des International College of Angiology, New York. Stuttgart, 1959, Georg Thieme Verlag, 811 pages, 373 illustrations. Price: DM 174. U. S. and Canadian agents: Intercontinental Medical Book Corporation, New York, N. Y.

This book gives a detailed description of the entire field of peripheral vascular diseases.

In the first part, which deals with general problems, macroscopic, microscopic, and submicroscopic anatomy, and the physiology of the vascular system are mentioned, and the pathophysiology, pathologic anatomy, and problems concerning the etiology of the diseases of this system are described. Special emphasis is laid on such factors as coagulation, hemodynamic influences, blood chemistry, and general as well as local resistance mechanisms of the body. General and special possibilities of diagnosis are discussed in detail. The various ways of conservative and operative treatment are presented.

In the second part of the book, which deals with the different diseases, description is made of the several types of angioneuropathies and angio-organopathies in the different parts of the vascular system, the arteries, arterioles, capillary system, and venous and lympathic systems. Furthermore, the congenital vascular abnormalities are discussed. Finally, problems related to insurance questions are mentioned.

The book is very well illustrated, and reference is given to European as well as American literature, so that it can be recommended both to the practitioner and the specialist.

Announcements

THE INTERNATIONAL SOCIETY OF CYBERNETIC MEDICINE, constituted in 1958 with the participation of nineteen countries, held its first General Assembly in Naples, Italy, in November, 1959.

The Assembly elected the following officers: *President:* Professor Aldo Masturzo, of Naples University. *Vice President:* Professor Paul Nayrac, of Lille University. *Members of the Council:* Professors N. Wiener, G. Asboe-Hansen, F. Nember, A. Gata, and C. Coruzzi.

It was decided to organize in Naples, in 1960, an International Symposium on Cybernetic Medicine, with the participation of Prof. Norbert Wiener.

The Council has confirmed the office of Secretary-General, Via Roma 348, Naples, Italy.

THE INTERNATIONAL ASSOCIATION OF GERONTOLOGY has selected San Francisco, Calif., as the site for its Fifth International Congress of Gerontology. The dates will be Aug. 7 to 12, 1960. On the basis of the interest already shown in the Congress, it is expected that between 1,500 and 2,000 persons, from every continent, will participate in the Congress.

The program of the Congress will be planned in four sections: The Biological Sciences; Clinical Medicine; Psychology and the Social Sciences; and Social Welfare. Each section will hold six scientific sessions for the presentation of papers. These four scientific sessions will meet simultaneously. Each section's program committee will be responsible for planning a general symposium to be attended by all Congress participants. In addition there will be two plenary sessions and at least one open, public meeting. In order to allow the widest possible latitude for the scientific papers, there will be no over-all Congress theme. English will be the official language for the Congress.

There will be ample space immediately adjacent to the meeting rooms for exhibits. All enquiries relative to commercial or scientific exhibits should be addressed to: Dr. Leo Gitman, Chairman, Committee on Exhibits, Brooklyn Home for the Aged, Howard and Dumont Avenues, Brooklyn 12, N.Y., U.S.A.

All enquiries, except in regard to the submission of papers or to exhibits, should be directed to: Louis Kuplan, President, Fifth International Congress of Gerontology, Post Office Box 2103, Sacramento 10, Calif., U.S.A.

THE AMERICAN COLLEGE OF CARDIOLOGY will hold its ninth annual convention at the Claypool Hotel, Indianapolis, Ind., on May 23-28, 1960. Dr. Gabriel F. Greco, Ozone Park, N.Y., Chairman, Publicity Committee, has announced that the program will present a variety of topics of current interest in cardiology. Dr. Samuel A. Levine, Boston, will deliver the guest lecture on Some Prevalent Errors in the Practice of Cardiology. There will be a Symposium on Recent Advances in the Treatment of Congestive Heart Failure, with prominent speakers covering physiology, pharmacology, changing mechanisms, fluids, electrolytes, cardiac glycosides, and other measures. Scientific sessions will be devoted to Surgical Management of Coronary Artery Diseases, with emphasis on criteria for the selection of patients, and availability of surgical methods for the improvement of collateral circulation. There will be a Survey of the Diagnosis and Treatment of Congenital Heart Diseases, with an analysis of diagnostic methods, surgical treatment, and end results in

the cyanotic and acyanotic groups. Cardiovascular Response to Stress will be considered by several outstanding scientists and clinicians. There will be panel discussions and scientific exhibits. The popular Fireside Conferences will gather around well-known preceptors for open discussions of current problems in cardiology. Dr. Osler A. Abbott, Atlanta, President of the College, will preside at the sessions. Dr. John S. LaDue, New York, is the dynamic Chairman of the Program Committee, who has prepared a program offering the greatest investment value of time to those planning to attend.

Full information on the meeting may be obtained from Dr. Philip Reichert, Executive Director, Empire State Building, New York 1, N.Y.

A COURSE IN ELECTROCARDIOGRAPHIC INTERPRETATION FOR GRADUATE PHYSICIANS will be given at the Michael Reese Hospital by Louis N. Katz, M.D., and Alfred Pick, M.D. (respectively, Director and Associate Director of the Cardiovascular Department), and Associates. The class will meet daily from 9:00 A.M. to 5:00 P.M., July 18 through 30, 1960.

Further information may be obtained from Miss Beverley Petzold, Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital and Medical Center, Chicago 16, Ill.

THE ELEVENTH ANNUAL FISK UNIVERSITY INFRARED SPECTROSCOPY INSTITUTE will be held at Fisk University, Nashville, Tenn., from Aug. 3 through 12, 1960.

The 1960 Fisk Infrared Institute, as planned by Directors Nelson Fuson, Ernest A. Jones, and James R. Lawson, will be divided into two separate sessions as follows: August 3 through 6—"Introduction to Infrared Spectroscopy: Elementary Theory and Experimental Techniques." August 8 through 12—"Interpretation of Infrared Spectra and Recent Developments in Infrared Techniques."

For further information write directly to Nelson Fuson, Director, Fisk Infrared Institute, Fisk University, Nashville, Tenn.

The San Francisco-Stanford Hospital in cooperation with the San Francisco Heart Association announces a postgraduate conference, "Vector-Electrocardiography: Vector Interpretation of the Conventional Electrocardiogram," on Saturday, May 28, 1960, 9 A.M. to 5 P.M. The guest speaker will be E. Grey Dimond, M.D., Professor of Medicine, University of Kansas Medical School.

For information, write to Arthur Selzer, M.D., San Francisco-Stanford Hospital, Clay and Webster Streets, San Francisco 15, Calif.

The University of Minnesota, Minneapolis, Minn., announces a Continuation Course for Physicians, entitled, "Cardiovascular Diseases for General Physicians and Specialists," to be held at the Center for Continuation Study, May 9-11, 1960.

The University of Minnesota announces a CONTINUATION COURSE IN INTERMEDIATE ELECTROCARDIOGRAPHY FOR GENERAL PHYSICIANS AND SPECIALISTS, which will be held at the Center for Continuation Study on the University campus from May 2 to 6, 1960. This course is intended primarily for physicians who are familiar with the basic principles of electrocardiographic interpretation and is to assist them in improving their ability to evaluate the more unusual and difficult electrocardiograms.

Guest speakers will include Dr. Henry J. L. Marriott, Associate Professor, Department of Medicine, University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, Md.; and Dr. Louis Wolff, Assistant Clinical Professor, Department of Medicine, Harvard Medical School, Boston, Mass. The remainder of the faculty will include members of the faculty of the University of Minnesota Medical School.

Lodging and meal accommodations are available at the Center for Continuation Study.